Non-Interventional Study Protocol 747-404/405

OBETICHOLIC ACID (OCA)

Replicate Studies Evaluating the Effectiveness of Obeticholic Acid on Hepatic Real-World Outcomes in Patients with Primary Biliary Cholangitis

(HEROES PBC)

Version 1.0: 24 January 2022

ClinicalTrials.gov Identifier: NCT05292872

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SPONSOR'S APPROVAL OF THE PROTOCOL

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1/24/2022

[redacted], MD

Date

[redacted]
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-404/405. Having fully considered all the information available, I agree that it is ethically justifiable to conduct this study according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, study protocol and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-404/405 and in accordance with the elements of Good Clinical Practice (CPMP/ICH/135/95) and the Declaration of Helsinki relevant to observational research, and all regulatory requirements for protection of human subjects in studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

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1. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; (6-ECDCA); INT-747; DSP-1747

Title of Study:

Replicate Studies Evaluating the Effectiveness of Obeticholic Acid on Hepatic Real-World Outcomes in Patients with Primary Biliary Cholangitis (HEROES PBC)

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Studied Period (years):	**Phase of Development:**
Estimated initial patient inclusion date 01 Jun 2015 Estimated date last patient observation: 31 Dec 2021	Phase 4

Objectives:

Primary Objective

To evaluate the effect of OCA treatment on time to the first occurrence of the composite endpoint of all-cause death, liver transplant, or hospitalization for hepatic decompensation in PBC patients in 2 data sources: Global PBC registry and Komodo Health claims database.

Exploratory Objectives:

To evaluate the effect of OCA treatment on time to the first occurrence of individual components of the composite endpoint (outlined below):

- All-cause death
- Liver transplant
- Hospitalization for hepatic decompensation based on the first occurrence of:
  - Variceal bleed
  - Ascites (including hepatic hydrothorax and spontaneous bacterial peritonitis)
  - Hepatic encephalopathy

Methodology:

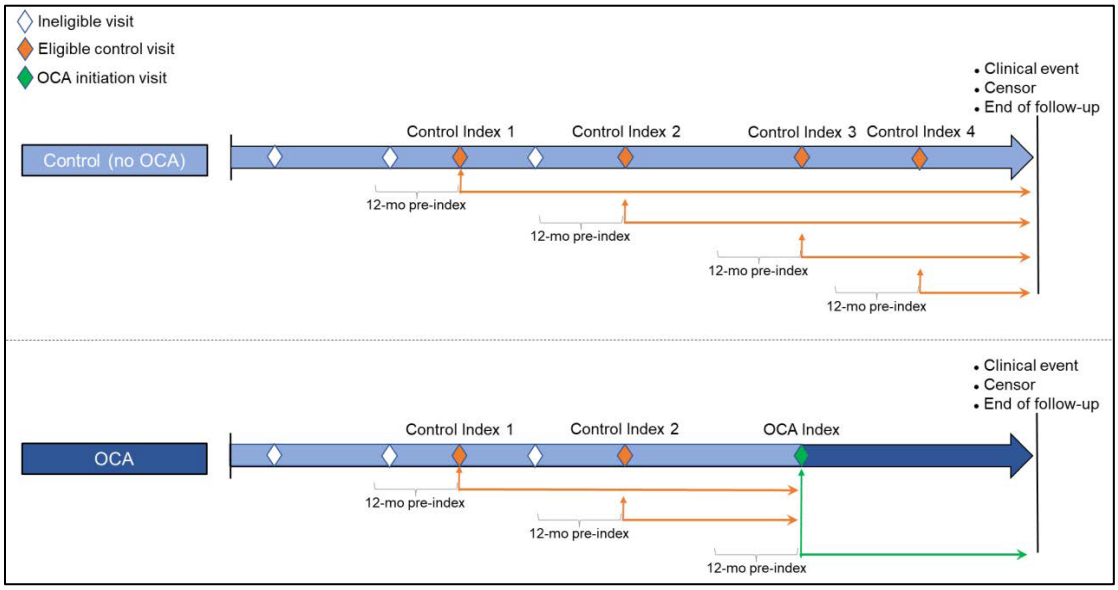
These are replicate, observational, retrospective cohort studies of patients with PBC who failed ursodeoxycholic acid (UDCA) treatment using 2 real-world data sources: the Global PBC registry (Study 747-404) and the Komodo Health United States (US) claims database (Study 747-405). All analyses will be conducted separately by data source (ie, not pooled). The primary endpoint is time to first occurrence of all-cause death, liver transplant, or hospitalization for hepatic decompensation. The analytic approach is a nested target trial emulation design.

The Komodo Health database contains administrative claims from >350 US payers, including commercial (63%); Medicaid (23%); Medicare (10%); dual eligible (<1%); and other (2%). Data are tokenized to allow for patient tracking across payers. Komodo Health claims will be linked through Datavant tokenization to Quest Diagnostics and LabCorp laboratory data, the US National Death Index (NDI), and the Organ Transplant Network (OPTN) transplant registry for additional information and outcome verification. The database contains >100,000 patients with a PBC diagnostic code. The Global PBC registry includes >5,000 patients with PBC recruited from 17 liver centers across 8 countries in Europe and North America. It utilizes the CASTOR trial platform for electronic case report form (eCRF) collection of medical history, clinical events, and laboratory and treatment data.

All patients who meet diagnostic criteria for PBC in each database between 01 Jun 2015 and 31 Dec 2021 and who meet all eligibility criteria will be considered for these studies. The OCA treatment evaluation period will be from 01 Jun 2016 (based on first country approval by Food and Drug Administration on 27 May 2016). The Komodo Health database is US-specific and the Global PBC registry includes the US and multiple other countries with later approval dates. The Sponsor has applied the date of first global approval of 01 Jun 2016 for both studies. The first date of prescription of OCA after inadequate UDCA response (ALP>upper limit of normal [ULN] and/or total bilirubin [TB]>ULN after >270 days of treatment) or UDCA intolerance (discontinued UDCA after <90 days despite ALP>ULN and/or TB>ULN) will be defined as the index date for OCA-treated PBC patients. The dates of evidence of inadequate UDCA response or UDCA intolerance during which OCA is not utilized will be used as an index date for the non–OCA-treated comparator group.

Each time a patient meets the UDCA inadequate response/intolerance definition or the definition of OCA initiation, in addition to all other eligibility criteria, they will contribute an index to the study. Therefore, patients may contribute multiple control indices, and may contribute control indices before OCA initiation, but can contribute only one OCA initiation index. The non–OCA-treated patient indices will be weighted to have the same baseline covariate distribution as the OCA-treated patients at the time of OCA initiation, thus allowing for the estimation of the effect of treatment in the treated patients. The pre-index period is defined as 12 months prior to the index date, and follow-up is until the first occurrence of any component of the composite endpoint. Patients will be censored at dropout/disenrollment from the database, discontinuation of OCA (+90 days), initiation of fenofibrate or bezafibrate, initiation of OCA (for the non–OCA-treated patient -indices), unapproved OCA dose (>10 mg once daily [QD]) for those treated with OCA, or the end of the study period (31 Dec 2021), whichever comes first.

Schematic Diagram Studies 747-404/405:



Number of Patients (planned):

Komodo Health: In the current Komodo Health database, there are 395 patients who meet all of the following criteria for the OCA treatment group:

- Meet PBC claims diagnostic criteria (1 inpatient or 2 outpatient claims)
- Have evidence of UDCA failure
- Have initiated OCA treatment

There are 5916 patients who meet all of the following criteria for the control group (OCA-eligible but not currently OCA-treated)

- Meet PBC claims diagnostic criteria (1 inpatient or 2 outpatient claims)
- Have at least 270 days of UDCA use before elevated ALP and/or TB inclusive of up to 4 instances of elevation (inadequate response) or <90 days UDCA use despite elevated ALP and/or bilirubin (intolerant)
- Have elevated ALP >ULN and/or TB >ULN

The Komodo Health database has not yet been linked to LabCorp laboratory database. It is anticipated that the number of patients in each group will approximately double with the availability of LabCorp data.

Global PBC registry: The Global PBC registry data are currently being refreshed. A previous analysis identified 344 patients who had initiated OCA. Among the >5000 patients not treated with OCA, it is anticipated that >2200 will meet criteria for UDCA failure and for inclusion in the control group (Corpechot 2008, Kumagi 2010).

Diagnosis and Main Criteria for Inclusion:

The treatment group will be patients with PBC with a history of inadequate response or intolerance to UDCA who initiated OCA in the study window. The control group will be PBC patients with a history of inadequate response or intolerance to UDCA who were eligible but not treated with OCA (or off-label fibrates) in the study window.

Key Inclusion Criteria

A patient who meets **all** of the following criteria for a given index date is eligible for inclusion:

- Definite or probable PBC diagnosis
  - Global PBC registry (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009, EASL 2009): presence of ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer
    - Liver biopsy finding consistent with PBC
  - Komodo Health claims data: one of the following (Meyers 2010):
    - ≥1 inpatient claim with a PBC admission diagnosis at any position (ie, primary, secondary diagnosis, etc.)
    - ≥2 outpatient claims with a PBC diagnosis on separate days
- Inadequate response or intolerant to UDCA (see definitions below)
- Age ≥18 years at the index date
- Continuous enrollment and evaluable data for at least 12 months before the index date (inclusive)

Key Exclusion Criteria:

A patient who meets **any** of the following criteria for a given index date is not eligible for inclusion:

- History or presence of the following concomitant liver diseases before the index date (inclusive), including:
  - Acute or chronic hepatitis C virus infection
  - Acute or chronic hepatitis B infection
  - Primary sclerosing cholangitis
  - Active alcoholic liver disease
  - Hepatocellular carcinoma
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Portopulmonary syndrome
  - Nonalcoholic steatohepatitis (NASH)
- History of non-skin malignancy or melanoma before the index date (inclusive)
- History of HIV before the index date (inclusive)
- Medical conditions that may cause non-hepatic increases in ALP such as:
  - Paget's disease during the 12-month period before the index date (inclusive)
  - Fractures within 3 months before the index date (inclusive)

- Patients with laboratory values indicative of hepatic decompensation or significant hepatobiliary injury before the index date (inclusive)
  - TB >3 mg/dL
  - ALP >10x ULN
  - ALT and/or AST >10x ULN
- History of liver transplant before the index date (inclusive)
- Evidence of OCA, fenofibrate, or bezafibrate use before the index date (inclusive)
- History or presence of any of the following hepatic decompensating events before the index date (inclusive):
  - Variceal bleeding
  - Ascites
  - Hepatic hydrothorax
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy

Definitions:

- **UDCA failure:**
  - Inadequate response requires both of the following:
    - At least 1 measure of ALP>ULN and/or TB>ULN
    - ≥270 days of UDCA treatment prior to ALP and/or TB elevation
  - Intolerant:
    - A maximum of 90 days of UDCA use with ALP>ULN and/or TB >ULN

Group Assignments:

- **Treatment group (OCA-treated)**: ≥1 prescription or medical claim for OCA at or after UDCA failure date. The first date will be the one index date.
- **Control Group (Non-OCA-treated but eligible for OCA):** Each date corresponding to evidence of a patient meeting the definition of UDCA inadequate response or intolerance in which the patient meets the inclusion and exclusion criteria and does not initiate OCA will be an index date for the non–OCA-treated patient group. Patients may contribute indices to this group before they initiate OCA, but not after OCA index.

Study medication, Dosage and Mode of Administration:

OCA tablet, 5 mg to 10 mg, once daily, oral administration

Patients may down titrate to <5 mg daily, but are censored if dose exceeds 10 mg per day.

Study drug is not provided nor administered by the Sponsor but is recorded by either administrative claim or registry CRF.

Duration of treatment will range from 1 to 67 months

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Data Sources

The data source for each analysis will include one of the following:
1. Komodo Health US administrative claims database linked to the following:

- Laboratory measures (Quest Diagnostics and LabCorp)
- National Death Index (US NDI)
- National transplant registry (OPTN registry)

Or

2. Global PBC registry

Criteria for Evaluation:

Primary Outcome:

As-treated time to the first event of the composite endpoint of all-cause death, liver transplant, or hospitalization for hepatic decompensation, whichever occurs first.

Exploratory Outcomes:

As-treated time to the first occurrence of individual components of the composite endpoint:

- All-cause death
- Liver transplant
- Hepatic decompensation requiring hospitalization assessed through claims or registry CRF and defined as first occurrence of:
  - Variceal bleed
  - Ascites (including hepatic hydrothorax and spontaneous bacterial peritonitis)
  - Hepatic encephalopathy

Exposure Variable:

The exposure variable is the use of OCA initiated at the index date.

Covariates:

The following covariates/control variables will be assessed **in the pre-index period**, utilizing the value closest to the index date:

- Age at index date
- Sex
- Most recent liver biochemistry levels (TB, ALP, ALT, AST)
- Most recent platelet counts
- Time (in months) since UDCA failure
- Clinical evidence of portal hypertension (platelets <150,000 and/or non-bleeding varices)
- Cirrhosis
- Most recent Charlson Comorbidity Index Score
- Insurance type at index date (Komodo Health only)

Statistical Methods:

Analysis Populations

The statistical analysis of the HEROES PBC studies will follow a nested randomized trial emulation approach (Hernán 2008, Danaei 2013) using a treatment decision design to identify index events (Brookhart 2015). Due to the lack of randomization, non-randomized observational studies will instead be conducted, with the goal of mimicking the hypothetical randomized trial as closely as possible. All patients will be evaluated over time from the start of the study period to identify evidence of inadequate treatment response to UDCA. Each date of inadequate response identified in the data will be considered a treatment decision point, and that date will be considered an index date, with a corresponding record created in the analytic data for that patient index. Each patient can contribute multiple index dates and thus patient indices, corresponding to each date they have a treatment decision point, and therefore each patient may contribute person-time to multiple patient index records.

It is likely that OCA-treated and non–OCA-treated patient indices will differ on confounding variables, ie, variables that influence both treatment and outcome. To address differences in the covariate distribution between treatment groups, the Sponsor will first conduct descriptive analyses on all baseline variables (demographics, clinical characteristics, and treatment history) for the OCA-treated and non–OCA-treated groups at index. Standardized mortality/morbidity ratio (SMR) weights then will be used to create a pseudo-population of non–OCA-treated indices with the same covariate distribution as the OCA-treated patients at the time of OCA initiation (Sato 2003), and unweighted and weighted standardized mean differences will be computed.

Primary Analysis:

The objective of the primary analysis is to estimate the as-treated effect of OCA treatment versus non–OCA-based treatment on the composite endpoint of all-cause death, liver transplant, or decompensation requiring hospitalization. The primary analysis outcome will be assessed with the hazard ratio comparing the hazard of the first event of the composite endpoint among the OCA-treated patients and standardized morbidity ratio-weighted

non–OCA-treated PBC patient indices. The hazard ratio will be estimated using a Cox proportional hazards model. The nonparametric bootstrap will be used to estimate the standard error of the estimate, which will then be used to generate 95% CI for the hazard ratio and to perform a test of the hypothesis that the hazard ratio is equal to the null value of 1.

Exploratory Analysis:

The exploratory objectives are to estimate the effect of OCA treatment versus non-OCA treatment on each component of the composite endpoint (all-cause death, liver transplant, or hepatic decompensation). The exploratory analysis outcomes will be assessed with the subdistribution hazard ratio comparing the hazard of the first event of each element of the composite endpoint, separately, among the OCA-treated patients and standardized morbidity ratio-weighted non–OCA-treated PBC patient indices. For the endpoint of liver transplant, death will be treated as a competing event. For the endpoint of hepatic decompensation, death and liver transplant will be treated as competing events. The subdistribution hazard ratio will be estimated using a Fine-Gray proportional subdistribution hazards model. The nonparametric bootstrap will be used to estimate the standard error of the estimates, which will then be used to calculate 95% CI for the hazard ratio and perform a test of the hypothesis that the hazard ratio is equal to the null value of 1.

Sample Size Justification:

Using the expected sample size in the 2 populations, the Sponsor computed power to detect treatment effects (relative hazards) of varying sizes, estimated using Cox proportional hazards regression. Computations are based on the formulae of Schoenfeld 1983. To account for confounding control due to the application of IP weights, the Sponsor inflated the variance from the Schoenfeld formula using factors derived by Shook-Sa 2020. It was conservatively assumed just one control observation per patient. In the Komodo Health data, a preliminary investigation found that approximately 395 patients who meet entry criteria initiate OCA and that 5916 patients will contribute at least one record to the control group (UDCA nonresponders). In the Global PBC registry, the Sponsor expects to have 344 patients meeting entry criteria who initiate OCA, and 2200 who contribute at least one observation to the control group. Power in both cohorts was computed for relative hazards ranging from 0.5 to 0.9 with an alpha level of 0.05. The Sponsor considered baseline event rates during follow-up from 5% to 15% and variance inflation corresponding to mild confounding (VIF=1.05), moderate confounding (VIF=1.5), and strong confounding (VIF=2.0). In each study, power was plotted under these assumptions against a reference line of 80% power under moderate confounding (VIF=1.5).

Under mild confounding, both studies will be well-powered to detect an HR of 0.5. For moderate confounding, the Komodo Health study will be adequately powered to detect HR of 0.5 for event rates >6%. The Global PBC registry will be adequately powered to detect event rates >8%. Under strong confounding, the Komodo Health study will be adequately powered to detect HR of 0.5 for event rates >9%. The Global PBC registry will be adequately powered to detect event rates >11%. Power decreases for more moderate HRs. None of the studies under even the most favorable assumptions will be able to detect HRs of 0.9. The Sponsor notes that the assumptions made here are conservative; in particular, it is expected that many more than one control observation and that the addition of lab data from LabCorp to will substantially increase the size of both treatment groups in the Komodo Health study.

Subgroup Analyses:

The entire analysis will be repeated separately by patient race (Komodo Health only), age (categorical), sex, region, presence/absence of cirrhosis, and pre-/post-COVID. Because race is not completely captured in either database, these analyses will only include those with non-missing values for race.

Sensitivity Analyses:

- An analysis will be conducted in the Komodo database to assess the performance of a claims-based PBC definition with AMA test results as the gold standard.
- Quantitative bias analysis to quantify the sensitivity of the estimate to violations of the assumption of no unmeasured confounding.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Abbreviation or Specialist Term	Explanation
AASLD	American Association for the Study of Liver Diseases
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
AST	aspartate aminotransferase
CDCA	chenodeoxycholic acid
CRC	Clean Room Committee
CRO	Clinical Research Organization
CVD	cardiovascular disease
DB	double-blind
DMC	data monitoring committee
EASL	European Association for the Study of the Liver
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration
FXR	farnesoid X receptor
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
HIPAA	Health Insurance Portability and Accountability Act
INR	international normalized ratio
ITT	intent-to-treat
LLN	lower limit of normal
LTSE	long-term safety extension
MELD	Model for End-Stage Liver Disease
NASH	nonalcoholic steatohepatitis
NDI	National Death Index
OCA	obeticholic acid
OPTN	Organ Transplant Network

Abbreviation or Specialist Term	Explanation
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPV	positive predictive value
QD	once per day
RWE	real-world evidence
SDTM	Study Data Tabulation Model
SMD	standardized mean differences
SOP	standard operating procedure
TB	total bilirubin
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US	United States

4. INTRODUCTION

4.1. Overview of Disease State and OCA

Primary biliary cholangitis, (PBC) is a serious, life-threatening, cholestatic liver disease of unknown etiology that, without treatment, frequently progresses to hepatic fibrosis and eventual cirrhosis or hepatic decompensation and necessitates liver transplantation or results in death. PBC is a rare disease with a reported prevalence in the United States (US) of 40/100,000 (Kim 2000). PBC disproportionately affects women (with a female to male ratio of approximately 10:1) and is typically diagnosed in patients aged 40 to 60 years.

The only approved drug therapy for PBC has been the bile acid ursodeoxycholic acid (UDCA), a physiological constituent of human bile (Lindor 2009). While UDCA therapy had a marked effect on the treatment of PBC, up to 40% of patients showed a suboptimal response or no response to UDCA (Corpechot 2008, Kumagi 2010). Such patients were at significantly increased risk of a poor clinical outcome due to PBC disease progression. Obeticholic acid (OCA) is a farnesoid X receptor (FXR) agonist and a modified bile acid that is derived from the primary bile acid chenodeoxycholic acid (CDCA), the natural human FXR ligand. OCA (Ocaliva®) has received marketing authorization in the US, the European Union (EU), and several other countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In the US, Ocaliva is contraindicated in patients with decompensated cirrhosis (eg, Child-Pugh Class B or C), a prior decompensation event, complete biliary obstruction, or compensated cirrhosis with evidence of portal hypertension. Approval in the US and the EU was based on a surrogate endpoint (reduction in ALP), and as part of regulatory commitments in these regions, the following postmarketing studies were initiated: Study 747-302, a Phase 3b/4 study designed to prospectively obtain evidence to confirm clinical benefit in PBC subjects, and Study 747-401, a Phase 4 study designed to evaluate the pharmacokinetics (PK) and safety of OCA in PBC subjects with hepatic impairment. Both 747-302 and 747-401 terminated early, due to the challenges of recruitment and long-term retention of patients with a rare disease subsequent to Ocaliva regulatory approval. Changes to endpoints and statistical analysis plans to accommodate low recruitment, low events rates, and early termination may necessitate the need for clinical trial data to be supplemented with real-world evidence, with the goal of providing regulators with a more complete evidence package characterizing the efficacy and safety of OCA in patients with PBC.

4.2. Mechanism of Action of OCA

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses. OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease, such as PBC.

4.3. Nonclinical Experience with OCA

Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.

4.4. Clinical Experience with Obeticholic Acid

As of 03 May 2021, approximately 4438 subjects have received ≥1 dose of OCA. This estimation includes subjects from blinded ongoing studies. Of these subjects, 978 were healthy volunteers, 610 subjects had PBC, 72 subjects had primary sclerosing cholangitis, 7 subjects had biliary atresia, 41 subjects had diabetes mellitus with non-alcoholic fatty liver disease, 2697 subjects had nonalcoholic steatohepatitis (NASH), and 33 subjects had portal hypertension due to alcoholic cirrhosis.

As of 03 May 2021, the clinical pharmacology of OCA had been evaluated in 19 completed Phase 1 studies. Overall, the PK of OCA shows the profile expected of a natural bile acid. There is rapid absorption of unconjugated OCA (parent), followed by extensive conjugation to glycine and taurine to form glyco-OCA and tauro-OCA, respectively. Glyco-OCA and tauro-OCA occur at significantly higher concentrations than the parent drug does. There are numerous peak and trough plasma concentrations observed, consistent with the expected extensive enterohepatic circulation of a bile acid. Plasma concentrations dramatically increase shortly after food intake, consistent with the gall bladder emptying into the duodenum. The glyco-OCA and tauro-OCA conjugates of OCA are known to be pharmacologically active, and due to enterohepatic recycling of OCA and its conjugates, their plasma PK profiles are most relevant.

Data that supported approval of Ocaliva included 3 randomized, double-blind, placebo-controlled, multi-center, international studies in subjects with PBC:

- Study 747-201 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC whose disease was sub-optimally controlled. In this study, OCA doses of 10 mg and 50 mg were evaluated as monotherapies.
- Study 747-202 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC who were sub-optimally controlled. OCA doses of 10 mg, 25 mg, and 50 mg were evaluated as add-on therapy to UDCA, the current standard of care for PBC.

- Study 747-301(POISE) was the pivotal Phase 3, 12-month, international, double-blind, placebo-controlled study in subjects with a proven or likely diagnosis of PBC whose disease was sub-optimally controlled. In this study, OCA doses evaluated were 10 mg or a titration approach (ie, 5 mg for the initial 6 months, with up-titration to 10 mg for the last 6 months if the subject did not meet the primary composite endpoint and had no tolerability issues).

In the double-blind, Phase 2 Studies 747-201 and 747-202, treatment with OCA for 3 months in subjects with PBC resulted in statistically and clinically significant reductions in ALP, a known surrogate for risk of long-term clinical outcomes in PBC, as well as markers of hepatic damage and inflammation. Consistent efficacy results were observed irrespective of whether OCA was administered as monotherapy or as an add-on to UDCA. Within each study, OCA doses above 10 mg did not show substantially better efficacy compared with OCA 10 mg, but the incidence and severity of pruritus were increased, suggesting that 10 mg was the maximally efficacious dose and that evaluation of lower doses in the Phase 3 program was warranted.

The Phase 3 study met its primary endpoint. Both OCA treatment groups (OCA titration and OCA 10 mg) were superior to placebo in achieving the primary endpoint at all timepoints across the 12-month treatment period ($p<0.0001$ versus placebo).

Each of these 3 studies included open-label, uncontrolled, long-term safety extension (LTSE) phases to evaluate the long-term effects of OCA treatment. As of 03 May 2021, the LTSEs of Studies 747-201, 747-202, and 747-301 are completed.

Study 747-301 LTSE: A total of 217 subjects were enrolled into the double-blind phase of the study; of the 198 subjects who completed the double-blind phase, 193 subjects (98%) enrolled into the LTSE phase. Overall, there was good retention in the study: 146 (76%) subjects completed the protocol as specified after administrative termination/closure of the study, and 47 (24%) subjects discontinued the LTSE prematurely. The majority of subjects discontinued because of study closure by the Sponsor. The efficacy associated with continued treatment with OCA up to 6 years was durable and consistent with the effects observed in the double-blind phase.

An additional 8-week, open-label study was also supportive of Ocaliva approval; however, efficacy data from this study were not integrated with Studies 747-201, 747-202, and 747-301 because of differences in study design and endpoints:

- Study 747-205 assessed the safety, tolerability, and pharmacodynamic (PD) effects of OCA on high-density lipoprotein cholesterol metabolism in subjects with PBC on a stable dose of UDCA. The LTSE phase is considered complete the clinical study report approved 07 Jan 2021.

Postmarketing studies in subjects with PBC include the following:

- Study 747-302 (COBALT; postmarketing requirement) is a double-blind, randomized, placebo-controlled, multicenter study designed to prospectively obtain evidence to confirm clinical benefit and further evaluate the benefit-risk profile of OCA treatment in subjects with PBC. Last Patient Last Visit occurred on 23 Dec 2021.

- Study 747-401 (postmarketing requirement) is a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in subjects with PBC and moderate to severe hepatic impairment. This study was closed as of 09 Jul 2021.

4.5. Rationale for Study Design and Dose for OCA

4.5.1. Rationale for Study Design

Studies 747-404 and 747-405 are replicate, observational, retrospective cohort studies. In rare diseases, real-world retrospective observational studies utilizing claims and registry data have been recognized by the US Food and Drug Administration (FDA) as viable for various regulatory use-cases, including constructing of external control arms for clinical trials (US Food and Drug Administration 2018, US Food and Drug Administration 2021).

The analytic approach, a nested randomized trial emulation using a treatment decision design to identify index events (Hernán 2008, Danaei 2013, Brookhart 2015), was selected to best mimic a clinical trial and has been shown to replicate trial results in epidemiologic data when other real-world approaches have not (Hernán 2008). This design emulates a sequence of hypothetical randomized trials, and, though non-randomized and non-blinded, mimics trial eligibility criteria, definition of start of follow-up, and treatment arms (initiators vs. non-initiators). Standardized morbidity ratio-weighting is used to adjust for imbalances in patient characteristics at index. The approach will produce an average hazard (rate) ratio (HR) and 95% confidence interval, comparing OCA initiators to non-initiators, thus yielding the standard output of a clinical study that is amenable to statistical hypothesis testing (ie, null hypothesis: HR=1). An as-treated approach was deemed superior to an intent-to-treat (ITT) approach, as the ITT approach in epidemiological data often causes severe treatment misclassification, particularly in chronic disease (Hernán 2008).

4.5.2. Rationale for Dose

The Ocaliva prescribing information states that the approved dosing is 5 mg once daily (QD) with allowable up-titration to a maximal dose of 10 mg QD. Patients prescribed OCA will be censored if they exceed the maximal allowable daily dose. Down-titration (less than daily dosing) can be utilized in response to adverse events such as pruritus, and as such, patients dosed <5 mg QD will continue to be counted in the OCA-treated arm.

4.5.3. Rationale for Control Group

Using standardized eligibility criteria across treated and untreated patients and utilizing a standardized morbidity ratio–weighted-OCA eligible but non–OCA-treated comparator group will provide the best scientific comparative evidence of efficacy.

4.6. Summary of Safety with OCA

4.6.1. Clinical Trial Exposure and Safety Experience

As of 03 May 2021, approximately 6183 subjects have been enrolled in the development program for OCA. Approximately 4438subjects received ≥1 dose of OCA in clinical studies sponsored by Intercept and Sumitomo Dainippon Pharma Co., Ltd. (Intercept's former

development partner in China, Korea, and Japan). Of these, a total of 610 PBC subjects had received ≥1 dose of OCA in completed (Studies 747-201 Double-Blind [DB], 747-201 LTSE, 747-202 DB, 747-202 LTSE, 747-205 Primary Treatment Phase, 747-301 DB, and 747-301 LTSE), ongoing unblinded (Study 747-205 LTSE), or blinded (Studies 747-302 and 747-401) studies.

In the completed studies, the majority of subjects had at least 5 years of exposure to OCA, and a small subset were exposed for more than 7 years. A total of 421 (97%) of these subjects who received OCA experienced treatment-emergent adverse events (TEAEs) during the study, and 379 (88%) subjects experienced investigational product–related TEAEs. Although the rate of TEAEs was higher in OCA-treated subjects compared with placebo-treated subjects, the differences noted in these incidence rates may be at least partially due to cumulative exposure differences between OCA and placebo. The most frequently reported TEAEs by System Organ Class in subjects receiving OCA were those classified as skin and subcutaneous tissue disorders (84%), gastrointestinal disorders (62%), and infections and infestations (56%). The most frequently reported (≥20% of subjects) individual TEAEs were pruritus (80%) and fatigue (26%).

While studies were ongoing, the data monitoring committee (DMC) convened at least every 6 months to review safety data for ongoing, double-blind, placebo-controlled postmarketing requirement studies 747-302 and 747-401. On 25 Mar 2020, the DMC recommended that both studies continue without modifications, consistent with prior periodic reviews. On 28 Sep 2020, the DMC reviewed a planned interim efficacy analysis for Study 747-302. The DMC noted that based on their review, they did not have additional analyses to suggest to better understand the observed hazard rate. They also noted that it did not seem feasible to continue the study as designed. On 18 Dec 2020, the DMC reviewed a planned in-depth analysis of unblinded safety data from Studies 747-302 and 747-401. Enrollment and retention were particularly poor in Study 747-302 in subjects with decompensated cirrhosis at baseline. Poor retention was also observed in Study 747-401, which is exclusively focused on subjects with CP-B and CP-C cirrhosis at baseline. The DMC noted a high likelihood of futility and difficulty in differentiating the etiology of hepatic safety events (OCA-related or progression of underlying disease). No safety concerns were raised by the DMC for either study. The DMC recommended stopping further enrollment in Studies 747-302 and 747-401 and discussing the unblinding of both studies with regulators. On 17 Feb 2021, the DMC recommended that both studies continue with modification. Due to the high likelihood of futility, the DMC recommended no further enrollment in the studies. On 09 Jun 2021, no additional modifications to the study were recommended. The DMC's previous recommendations remained unchanged (ie, continue discussion with regulatory authorities regarding unblinding). Following the United States Prescribing Information update on 26 May 2021, Study 747-401 was closed as of 09 Jul 2021. On 03 Nov 2021, after careful consideration of feedback from the DMC and the FDA, Intercept terminated Study 747-302 with Last Patient Last Visit completed on 23 Dec 2021.

4.6.2. Known and Potential Risks of OCA

The risk profile of OCA use in PBC has been evaluated in clinical trials and observational studies, as well as from postmarketing experience (estimated cumulative patient exposure from marketing experience is 20,554 patient-years). The key risk for OCA is pruritus. Potential risks

include liver injury and atherosclerotic cardiovascular events secondary to changes in lipids. The following focuses on these risks in the context of PBC, the subject of these current studies. Additional information is available in the Investigator's Brochure.

Pruritus: In subjects with PBC, the most commonly reported TEAE across all treatment groups was pruritus, which is a frequent symptom experienced by subjects with cholestatic liver disease. The incidence of pruritus was higher in the OCA-treated subjects as compared with placebo-treated subjects. In a small proportion of patients, pruritus can be severe and significantly interfere with sleep and patient functioning. Patients with a history of pruritus as part of the underlying disease have a higher probability of pruritus with OCA treatment. Otherwise, the occurrence and severity of pruritus in an individual patient treated with OCA cannot be reliably predicted or prevented, in part because pruritus is a frequent clinical feature of the underlying disease. Pruritus has also been seen in patients participating in clinical trials of investigational use of OCA, including NASH, where pruritus is not a common symptom of the disease state. Pruritus is generally clinically manageable. Reducing OCA dose or transient dose or transient treatment interruption helps alleviate, and in some cases, even resolves it.

Liver Injury: Liver injury is an important potential risk for OCA. Risk factors for drug-induced adverse hepatic effects are in general poorly understood in patients with chronic liver disease. Pre-existing liver disease may not increase the risk of developing drug-induced liver injury (Chalasani 2014). In the US, OCA is contraindicated in adult patients with PBC with decompensated cirrhosis or a prior decompensation event and with compensated cirrhosis with clinical evidence of portal hypertension. OCA is also contraindicated in adult patients with PBC with complete biliary obstruction.

In two 3-month, placebo-controlled studies in subjects with PBC, a dose-response was observed for the occurrence of liver-related adverse reactions including jaundice, worsening ascites, and PBC flare with dosages of OCA 10 mg to 50 mg once daily (up to 5-times the highest recommended dosage in PBC). In a pooled analysis of 3 placebo-controlled studies in subjects with PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions and isolated elevations in liver biochemical tests, per 100 patient years of exposure were: 5.2 in the OCA 10 mg group, 19.8 in the OCA 25 mg group, and 54.5 in the OCA 50 mg group compared to 2.4 in the placebo group.

Atherosclerotic Cardiovascular Events Secondary to Changes in Lipids: This risk has been recognized as an important potential risk since OCA is associated with lipid profile changes, regardless of background disease state. Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol. A reduction in mean high-density lipoprotein and an increase in low-density lipoprotein with OCA treatment have been observed in patients with PBC. It is unknown whether these changes in lipids are associated with or are causally related to an increased risk of atherosclerotic cardiovascular disease (CVD) and associated morbidity and mortality in PBC patients, when compared with the general population. The lipid abnormalities may be managed in PBC patients receiving OCA, by monitoring and managing lipid levels and other CVD risk factors.

5. STUDY OBJECTIVES AND PURPOSE

The overall objective of these studies is to evaluate the effectiveness of OCA on hepatic outcomes in patients with PBC who failed UDCA treatment in 2 real-world data sources: Global PBC registry and Komodo Health claims database.

5.1. Primary Objective

To evaluate the effect of OCA treatment on time to the first occurrence of the composite endpoint of all-cause death, liver transplant, or hospitalization for hepatic decompensation in PBC patients in 2 data sources: Global PBC registry and Komodo Health US claims database.

5.2. Exploratory Objectives

To evaluate the effect of OCA treatment on time to the first occurrence of individual components of the composite endpoint (outlined below):

- All-cause death
- Liver transplant
- Hospitalization for hepatic decompensation based on first occurrence of:
  - Variceal bleed
  - Ascites (including hepatic hydrothorax and spontaneous bacterial peritonitis)
  - Hepatic encephalopathy

6. INVESTIGATIONAL PLAN

6.1. Overall Design

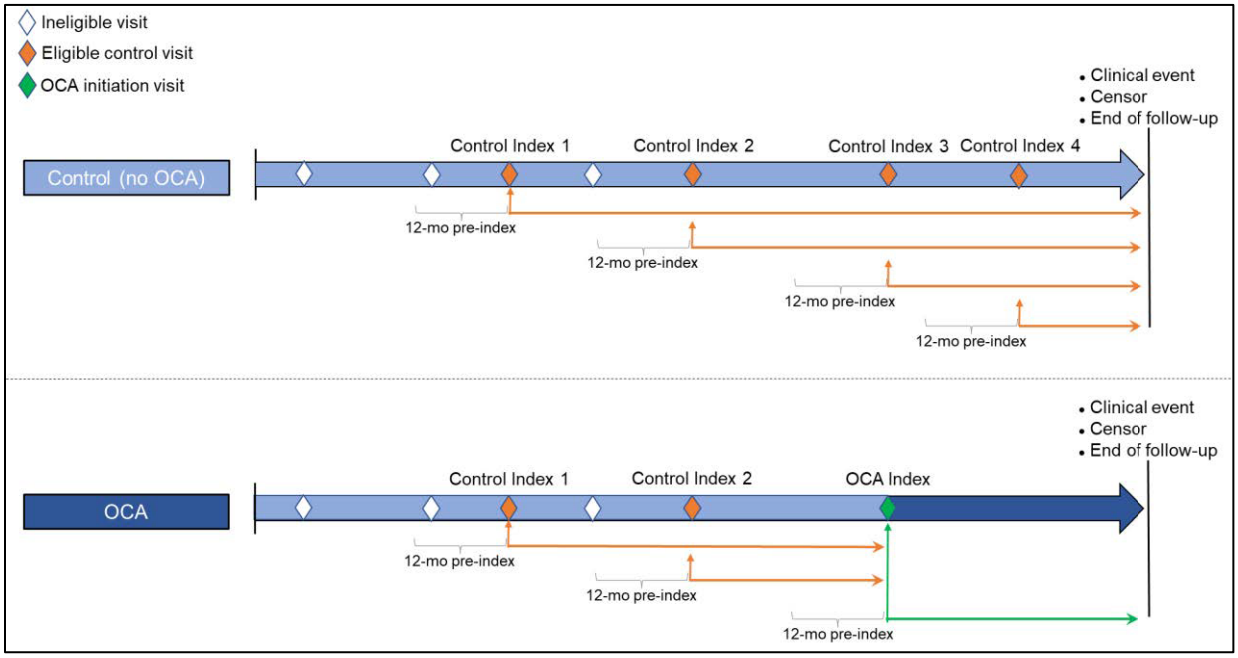
These are replicate, observational, retrospective cohort studies of patients with PBC who failed UDCA treatment using 2 real-world data sources: the Global PBC registry (Study 747-404) and the Komodo Health US claims database (Study 747-405). All analyses will be conducted separately by data source (ie, not pooled). The Komodo Health database will be linked for outcome verification and additional data collection through Datavant tokenization to Quest Diagnostics, LabCorp, the NDI, and the Organ Transplant Network (OPTN) registry.

All patients who meet diagnostic criteria for PBC in each database between 01 Jun 2015 and 31 Dec 2021 and who meet the eligibility criteria (Section 7.2 and Section 7.3) will be considered for these studies. See Figure 1 for the design schematic. The OCA treatment evaluation period will be from 01 Jun 2016 (based on first country approval by FDA on 27 May 2016). The Komodo Health database is US-specific, while the Global PBC registry includes multiple countries with a range of approval dates. The Sponsor has applied the date of first approval of a participating country, and thus 01 Jun 2016 will be used for both studies. The first date of prescription of OCA after failing UDCA treatment will be defined as the index date for OCA-treated PBC patients. The date of evidence of inadequate UDCA response or UDCA intolerance, as defined in Section 7.1, will be used as an index date for the non–OCA-treated comparator group. Each time a patient meets the UDCA inadequate response/intolerance

definition or the definition of OCA initiation, as well as all other inclusion criteria, they will contribute an index to the study. Therefore, patients may contribute multiple control indices, and may contribute control indices before OCA initiation, but can contribute only one OCA initiation index. The non–OCA-treated patient indices will be weighted to have the same baseline covariate distribution as the OCA-treated patients at the time of OCA initiation, thus allowing for the estimation of the effect of treatment in the treated. Patients must have 12 months of data preceding the index date (ie, the pre-index period) to establish the medical history and OCA eligibility and for the standardized morbidity ratio-weighting. Follow-up of patients will be until the first occurrence of the composite endpoint. Patients will be censored at drop out/disenrollment from the database, discontinuation of OCA (+90 days), initiation of fenofibrate or bezafibrate, initiation of OCA (for the non–OCA-treated patient indices), unapproved OCA dose (>10 mg QD) for those treated with OCA, or the end of the study period (31 Dec 2021); whichever comes first.

6.1.1. Design Diagram

Figure 1: Design Schematic Studies 747-404/405



6.2. Number of Patients

The Komodo Health database contains administrative claims from >350 US payers, tokenized to allow for patient tracking across payers. Komodo Health claims will be linked through Datavant tokenization to Quest Diagnostics and LabCorp laboratory data, the US National Death Index (NDI), and the Organ Transplant Network (OPTN) transplant registry for additional information and outcome verification. The database contains >100,000 patients with a PBC diagnostic code. The Global PBC registry includes >5,000 patients with PBC recruited from 17 liver centers across 8 countries in Europe and North America. It utilizes the CASTOR trial platform for

electronic case report form (eCRF) collection of medical history, clinical events, and laboratory and treatment data.

Komodo Health: In the current Komodo Health database, there are 395 patients who meet criteria for the OCA treatment group:

- Meet PBC claims diagnostic criteria (1 inpatient or 2 outpatient claims)
- Initiate OCA treatment
- Have evidence of UDCA failure

There are 5916 who meet criteria for the control group (OCA-eligible but not currently OCA-treated)

- Meet PBC claims diagnostic criteria (1 inpatient or 2 outpatient claims)
- Have at least 270 days of UDCA use before elevated ALP and/or TB inclusive of up to 4 instances of elevation (inadequate response) or ≤90 days UDCA use before elevated ALP and/or TB (intolerant)
- Have evidence of ALP >ULN and/or TB >ULN

The Komodo Health data have not yet been linked to LabCorp laboratory data. It is anticipated that these numbers will approximately double with the availability of LabCorp data.

Global PBC Registry: The Global PBC registry data are currently being refreshed. A previous analysis identified that 344 patients who had initiated OCA. Among the >5000 patients not treated with OCA, it is anticipated that >2200 will meet criteria for UDCA failure and for inclusion in the control group (Corpechot 2008, Kumagi 2010).

7. SELECTION OF PATIENTS

7.1. Study Population

All patients who meet diagnostic criteria in each database between 01 Jun 2015 and 31 Dec 2021 and who meet the eligibility criteria will be considered for these studies.

All diagnosis, treatment, laboratory, and procedure codes used to identify patients and define study variables are listed in Appendix A.

The treatment group will be patients with PBC with a history of inadequate response or intolerance to UDCA who initiated OCA in the study window. The control group will be PBC patients with a history of inadequate response or intolerance to UDCA who were eligible but were not treated with OCA (or off-label fibrates) in the study window. The decision to treat a patient with OCA or UDCA is at the discretion of the treating physician and has been made independent from inclusion in each of the databases.

7.1.1. Definition of UDCA Failure

UDCA failure includes both inadequate response to UDCA, and intolerance to UDCA. Inadequate UDCA response is defined as:

- At least 1 measure of ALP and/or TB >ULN; and
- ≥270 days of UDCA treatment prior to ALP and/or TB elevation

UDCA intolerance is defined as:

- A maximum of 90 days of UDCA use with ALP>ULN and/or TB >ULN.

The first date of prescription of OCA after inadequate UDCA response (ALP>upper limit of normal [ULN] and/or total bilirubin [TB]>ULN after >270 days of treatment) or UDCA intolerance (discontinued UDCA after <90 days despite ALP>ULN and/or TB>ULN) will be defined as the index date for OCA-treated PBC patients. The dates of evidence of inadequate UDCA response or UDCA intolerance during which OCA is not utilized will be used as index dates for the non–OCA-treated comparator group.

7.2. Inclusion Criteria

A patient who meets **all** of the following criteria for a given index date is eligible for inclusion:

- Definite or probable PBC diagnosis
  - Global PBC Registry (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009, EASL 2009): presence of ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer
    - Liver biopsy finding consistent with PBC
  - Komodo Health claims data: one of the following (Meyers 2010):
    - ≥1 inpatient claim with a PBC admission diagnosis at any position (ie, primary, secondary diagnosis, etc.)
    - ≥2 outpatient claims with a PBC diagnosis on separate days
- Inadequate response or intolerance to UDCA (see definitions in Section 7.1)
- Age ≥18 years at the index date
- Continuous enrollment and evaluable data for at least 12 months before the index date (inclusive)

7.3. Exclusion Criteria

A patient who meets **any** of the following criteria for a given index date is not eligible for inclusion:

- History or presence of other concomitant liver diseases before the index date (inclusive), including:
  - Acute or chronic hepatitis C virus infection
  - Acute or chronic hepatitis B infection

  - Primary sclerosing cholangitis
  - Active alcoholic liver disease
  - Hepatocellular carcinoma
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Portopulmonary syndrome
  - NASH
- History of non-skin malignancy or melanoma before the index date (inclusive)
- History of HIV before the index date (inclusive)
- Medical conditions that may cause non-hepatic increases in ALP:
  - Paget's disease during the 12-month period before the index date (inclusive)
  - Fractures within 3 months before the index date (inclusive)
- Patients with laboratory values indicative of hepatic decompensation or significant hepatobiliary injury before the index date (inclusive):
  - TB >3 mg/dL
  - ALP >10x ULN
  - ALT and/or AST >10x ULN
- History of liver transplant before the index date (inclusive)
- Evidence of OCA, fenofibrate, or bezafibrate use before the index date (inclusive)
- History or presence of any of the following hepatic decompensating events before the index date (inclusive):
  - Variceal bleeding
  - Ascites
  - Hepatic hydrothorax
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy

7.4. Group Assignments

Treatment group (OCA-treated): ≥1 prescription or medical claim for OCA at or after UDCA failure date. The first date will be the one index date.

Control Group (Non-OCA-treated but eligible for OCA): Each date corresponding to evidence of a patient meeting the definition of UDCA inadequate response or intolerance in which the patient meets the inclusion and exclusion criteria and does not initiate OCA will be an

index date for the non–OCA-treated patient group. Patients may contribute indices to this group before they initiate OCA, but not after OCA index.

A thorough description of methodology underlying group assignment can be found in Section 10.1.1.

7.5. Study Product, Dosage and Mode of Administration

The product being studied is obeticholic acid, in tablet form, dosed at 5 mg to 10 mg once daily oral administration. The study drug is not provided nor administered by the Sponsor but is recorded by either administrative claim or registry eCRF. The total duration of exposure will range from 1 to 67 months.

7.6. Study Period

The total study period is estimated to be a maximum of 6.6 years based on a pre-index period of 12 months prior to the index date and a maximum follow-up period of 5.6 years after the index date. The OCA treatment evaluation period will be from 01 Jun 2016 (based on FDA approval on 27 May 2016) to 31 Dec 2021. The first date of prescription of OCA after failing UDCA treatment will be defined as the index date for OCA-treated PBC patients. The date of evidence of inadequate UDCA response or UDCA intolerance, as defined below, will be used as the index date for the non–OCA-treated comparator group. Each time a patient meets the UDCA inadequate response/intolerance definition or the definition of OCA initiation, as well as all other inclusion/exclusion criteria, they will contribute an index to the study. Therefore, patients may contribute multiple indices and may appear in both groups, though they may contribute at most one index to the OCA-treated group.

8. ASSESSMENT OF EFFICACY

8.1. Primary Outcomes/Endpoints

The selection of a composite primary endpoint was informed by previous regulatory interactions regarding the 747-301 (POISE) and 747-302 (COBALT) studies (see Table 1). For COBALT, the primary composite endpoint included all-cause death, liver transplant, hospitalization for hepatic decompensation (bleeding varices and hepatic encephalopathy), uncontrolled ascites, and Model for End-Stage Liver Disease (MELD) Score $\geq$15. Of these endpoints, only MELD cannot be adequately assessed in the current databases. The MELD algorithm includes a measure of the international normalized ratio (INR). A review of the Komodo Health and the Global PBC registry databases revealed that, unlike hepatic laboratory measures such as ALP and TB, INR is not routinely collected in PBC patients. Therefore, the Sponsor did not include MELD $\geq$15 as part of the composite endpoint for these studies.

COBALT included the endpoint of uncontrolled ascites, defined as diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month. In a study of the POISE LTSE with external controls (Perez 2021), the Sponsor modified this endpoint to be consistent with other decompensating events, ie, hospitalization for ascites. As the FDA Guidance on Real-world Data (US Food and Drug Administration 2021) states, "…*outpatient data sources that do not include hospitalization data would generally not be appropriate for studying outcomes likely to result in hospitalization.*" To increase consistency in the measures of

hepatic decompensating events, the Sponsor has included ascites (including hepatic hydrothorax and spontaneous bacterial peritonitis), along with variceal bleeding and hepatic encephalopathy, as part of the "hospitalization for hepatic decompensation" endpoint.

Table 1: Composite Endpoints for OCA PBC Studies

	COBALT (747-302)	POISE (747-301) LTSE with External Controls	HEROES PBC (747-404/405)
All-cause death	X	X	X
Liver transplant	X	X	X
Hospitalization for hepatic decompensation • Variceal bleed • Hepatic encephalopathy	X	X	X
Uncontrolled ascites	X	X[a]	X[a]
MELD Score ≥15	X		

[a] Specifies hospitalization for ascites

The following primary efficacy assessment will be measured as an as-treated time to first occurrence of one of the following events:

- All-cause death
  - Komodo Health: The Komodo Health data has been linked to the US National Death Index (NDI), and mortality will be recorded as date of death as recorded in the Index
  - Global PBC registry: Death and date of death are reported by the physician via electronic Case Report Form (eCRF) and recorded through the CASTOR trial platform
- Liver transplantation
  - Komodo Health: The Komodo Health data will be linked to the OPTN database to ascertain whether a patient has received a liver transplant and the date of transplant.
  - Global PBC registry: Liver transplant and date of transplant are reported by the physician via eCRF and recorded through the CASTOR trial platform.
- Hospitalization for hepatic decompensation
  - Komodo Health: Hospitalization for hepatic decompensation will be assessed by any hospital admission claim with the following International Classification of Diseases (ICD)-10 codes (in any position) for decompensating events
    - Variceal bleed: ICD-10: I85.01, I85.11, I86.4 and ICD-9: 456.1, 456.21, 456.8
    - Ascites: ICD-10: K70.11, K70.31, K71.51, R18.0, R18.8, J94.8, K65.2 and ICD-9: 567.23, 571.2, 789.51,789.59, 511.8, 567.23

- Hepatic encephalopathy: ICD-10: B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, K70.41, K72.11, K72.90, K72.91 and ICD-9: 572.2, 070.0, 070.20, 070.41, 070.6, 070.71; or utilization of lactulose and/or rifaximin.

– Global PBC registry: Hospitalization for hepatic decompensation and date of hospitalization are reported by the physician via eCRF and recorded through the CASTOR trial platform

8.2. Exploratory Outcomes

There will be 3 exploratory evaluations of efficacy, measured as the as-treated:

– Time to first occurrence of all-cause death

– Time to first occurrence of liver transplant

– Time to first occurrence of hospitalization for hepatic decompensation

8.3. Exposure Variable

The exposure variable initiates at the OCA index date. In the Komodo database, OCA exposure will be assessed as date of first filled prescription and quantified as days supply. Discontinuation will be assessed by a gap of >90 days after previous days supply. Treatment exposure will be continued for 90 days after last days supply, after which the OCA-treated patient will be censored. In the Global PBC database, OCA exposure will be from the first physician reported utilization date to discontinuation date, plus 90 days. In this study, exposure can range from 1 to 67 months.

9. ASSESSMENT OF SAFETY

The objective of these replicate observational Real-world Data studies is to evaluate the effective of OCA on hepatic outcomes in patients with PBC. All patients are de-identified in the data sources. These studies are not designed to assess safety, and there are no pre-specified safety analyses. Study outcome variables collected for the 2 cohorts will be presented for analyses as aggregate data groups. The data sources will not be searched for individual patient adverse events; however, if an Investigator or Sponsor identifies adverse events that meet postmarketing reporting requirements during the course of conducting these studies, such events will be reported in accordance with applicable postmarketing reporting requirements.

10. STATISTICAL METHODS

10.1. Analysis Populations and Blinding

10.1.1. Analysis Populations

The statistical analysis of the HEROES PBC studies will follow a nested randomized trial emulation approach (Hernán 2008, Danaei 2013) using a treatment decision design to identify index events (Brookhart 2015). The goal of the study design is to emulate a sequence of hypothetical randomized trials. In each hypothetical trial, patients meeting the inclusion and exclusion criteria who are making the decision whether to initiate OCA-based treatment are

randomized to either continue their existing PBC treatment or switch to an OCA-based treatment. Each randomized patient is then followed until the earliest of the end of follow-up or the time of the study endpoint (death, liver transplant, or hospitalization for hepatic decompensation). Standard survival analysis methods (eg, a Kaplan-Meier estimator of the cumulative incidence function or a Cox proportional hazards model to estimate the hazard ratio) will then be used to estimate the effect of OCA on the study endpoint.

Due to the lack of randomization, non-randomized observational studies will instead be conducted, with the goal of mimicking the hypothetical randomized trial as closely as possible. All patients will be evaluated over time from the start of the study period to identify evidence of inadequate treatment response to UDCA. Each date of inadequate response identified in the data will be considered a treatment decision point, and that date will be considered an index date, with a corresponding record being created in the analytic data for that patient index. Each patient can contribute multiple index dates, and thus patient indices, corresponding to each date they have a treatment decision point, and therefore each patient may contribute person-time to multiple patient index records.

At each treatment decision point, the inclusion and exclusion criteria will be assessed (see Sections 7.2 and 7.3). For patient indices meeting the study criteria, all baseline covariates and treatment variables will be determined. Person-time corresponding to each patient index will be computed relative to the date of the index event. Notably, because prior treatment with OCA is an exclusion criterion, a patient may contribute at most one OCA-treated patient index event, though they can contribute multiple non–OCA-treated patient index events.

After the index date, follow-up will continue until the first of the composite outcome event (all-cause death, liver transplant, or hepatic decompensation), censoring, treatment discontinuation (for patient indices initiating OCA on the index date), OCA initiation (for patient indices not initiating OCA on the index date), or the end of the study period.

Because treatment will not be randomized, it is likely that OCA-treated and non–OCA-treated patient indices will differ on confounding variables, ie, variables that influence both treatment and outcome. Therefore, a simple comparison of outcomes among the OCA-treated versus non–OCA-treated patient indices is likely to yield a biased estimate of the effect of OCA on the study endpoint. To address differences in the covariate distribution between groups, the Sponsor will first conduct descriptive analyses on all baseline variables (demographics, clinical characteristics, and treatment history) for the OCA-treated and non–OCA-treated groups at index. Means, standard deviations, medians, inter-quartile ranges, and minimums and maximums will be provided for continuous variables. Counts and percentages will be provided for categorical variables. Appropriate tests comparing cohorts of interest in the primary and exploratory analyses (eg, t--test, chi-squared test) will be used based on the distribution of the measure.

Next, standardized mortality/morbidity ratio weights will be used to create a "pseudo-population" of non–OCA-treated indices with the same covariate distribution as the OCA-treated patients at the time of OCA initiation (Sato 2003), and unweighted and weighted standardized mean differences (SMDs) will be computed. SMR weights result in an average effect of treatment among the treated. They often make more efficient use of data in a situation with a small treatment group compared with inverse-probability of treatment weights. The SMR weights will be estimated as:

$w_i^t = \frac{\hat{\pi}_i(1)}{\hat{\pi}_i(A_i)}$, where w_i^t is the weight for patient index i, A_i is the observed level of treatment for patient index i ($A = 1$ if the patient index is OCA-treated, 0 otherwise), X_i is the vector of confounders measured at the index time for patient index i, and $\pi_i(a) = \Pr(A = a|X_i)$ is the probability that patient index i receives treatment level a conditional on their covariates.

As the probabilities used to construct the weights are not known, they will be estimated using a logistic regression model. The model will be fit using observed treatment as the outcome and main effect terms for each of the covariates. Covariates (assessed in the pre-index period) will include:

- Age at index date
- Sex
- Most recent liver biochemistry levels (TB, ALP, ALT, AST)
- Most recent platelet counts
- Time (in months) since UDCA failure
- Clinical evidence of portal hypertension (platelets <150,000 and/or non-bleeding varices)
- Cirrhosis
  - Komodo Health: cirrhosis diagnosis with liver imaging and/or biopsy within 6 months before diagnosis
  - Global PBC registry: biopsy stage 4, transient elastography ≥16.9 kPa, radiological evidence (nodular liver or enlargement of portal vein with splenomegaly), clinical features of portal hypertension defined as platelet count <140 000/mm³ with persistent decrease in serum albumin; or, TB >2x ULN, or prothrombin time/INR > ULN (not due to antithrombotic use)
- Most recent Charlson Comorbidity Index Score (Glasheen 2019)
- Insurance type at the index date (Komodo Health only: commercial, Medicare, Medicaid, dual eligible, other)

All diagnosis, procedure and laboratory codes used to define the control variables are listed in Appendix A.

Once the weights are constructed, a table of weighted SMDs between the groups will be constructed to assess balance. An absolute SMD of greater than 0.1 will indicate potentially problematic residual imbalance for the particular covariate. In the case that either the model-fitting algorithm fails to converge, or residual imbalance exists after weighting, the study team will attempt to reduce model complexity or reduce imbalances by implementing one or more of the following actions:

- Adding/removing interaction terms (1st order or higher)
- Using a spline for continuous variables
- Shrinking all coefficients in the model using a penalty

To protect the integrity of the research results, all decisions about updating the analysis will be made by the Investigators without knowledge of how those decisions might affect the outcome (Clean Room Committee [CRC], see Section 10.11). Each decision for a set of actions will be tracked in a study log along with the results presented to the analysis team to inform the action. The final weights will be used for the main analysis. Results for each stage of the developed weights will be documented and presented as supplementary material (and decisions will be recorded in the study log).

Under the identification conditions of causal consistency (Cole 2009, VanderWeele 2009, Pearl 2010), (partial) conditional exchangeability (Greenland 1986, Sarvet 2020), and positivity (Westreich 2010, Petersen 2012), the pseudo-population resulting from weighting the person-indices will emulate the data (at baseline) of the aforementioned hypothetical randomized trial.

10.1.2. Blinding

To ensure that knowledge of outcomes does not influence group creation, all persons involved in the studies will be kept blind to outcomes (death, liver transplant, hospitalization for decompensation) until after the analytic groups are created and the SMR weights are finalized. The event file will be kept separate from the primary data containing patient demographic, medical history, treatment, and laboratory data and will not be accessible to study personnel. Once the OCA-treated and non–OCA-treated datasets are created and approved by the CRC, the CRC will notify non–study-affiliated designees at each site that the event data can now be accessed in order to perform the effect size analysis and statistical testing.

10.2. Estimation of Effect Size

The causal effect of OCA-containing treatments versus non–OCA-containing treatments on the study endpoints will be quantified using a hazard ratio. The hazard ratio will be estimated using a weighted version of the sequential Cox proportional hazards model (Gran 2010). This approach entails fitting a weighted Cox proportional hazards regression to the person-index dataset, with weights created as previously described, treatment included as a non–time-varying indicator of baseline treatment, and the timescale being specified as time since the index event. In addition to adjusting for confounding via SMR weighting, baseline covariates for each person-index will also be included in the regression model to address possible informative censoring by baseline variables. To test for heterogeneity of effects across each of the nested ‘trials’, an interaction term between treatment and an indicator representing each trial will be included in the model. A non-significant coefficient for the interaction variables will indicate heterogeneity.

In randomized trials, a common approach to address imperfect treatment adherence is to censor patients when they deviate from their assigned treatment, a so-called per-protocol analysis (Hernán 2017). An analogous approach can be used for non-randomized observational studies. Here, a person-index is censored when they deviate from their initial treatment. For instance, if a person-index received non-OCA treatment at baseline but OCA was initiated 6 months after the index date, that person-index would be censored at 6 months. Similarly, if a person-index received OCA at baseline but discontinued OCA, that person-index would be censored once the definition of OCA discontinuation is met, with an extension of 3 months after that time to allow

for duration of effect after discontinuation. As a result of this artificial censoring, all person-time included in the analysis reflects adherence to initial treatment. Similarly, by excluding person-time occurring after loss to follow-up, all included person-time additionally reflects remaining time under study.

Because treatment non-adherence and loss to follow-up may not occur completely at random, those who remain uncensored may differ from the overall study population on key prognostic factors. To address these differences, the Sponsor will include baseline covariates in the Cox model that are potential predictors of both the study outcomes and censoring.

10.3. Hypotheses

10.3.1. Primary Hypothesis

These studies are intended to assess whether there is a difference between patients treated with OCA and comparable OCA-eligible patients who are not treated with OCA in the time from index to the first occurrence of all-cause death, liver transplant, or hospitalization for hepatic decompensation.

Two-sided hypotheses are expressed in terms of:

- The null hypotheses (H_0) that the 2 hazard functions are the same, as determined by a hazard ratio (HR) equal to 1; that is, at every timepoint, the instantaneous event rates are the same for the OCA and control populations.
- The alternative hypothesis (H_1) that the 2 hazard rates are not the same ($HR \neq 1$).

10.4. Determination of Sample Size

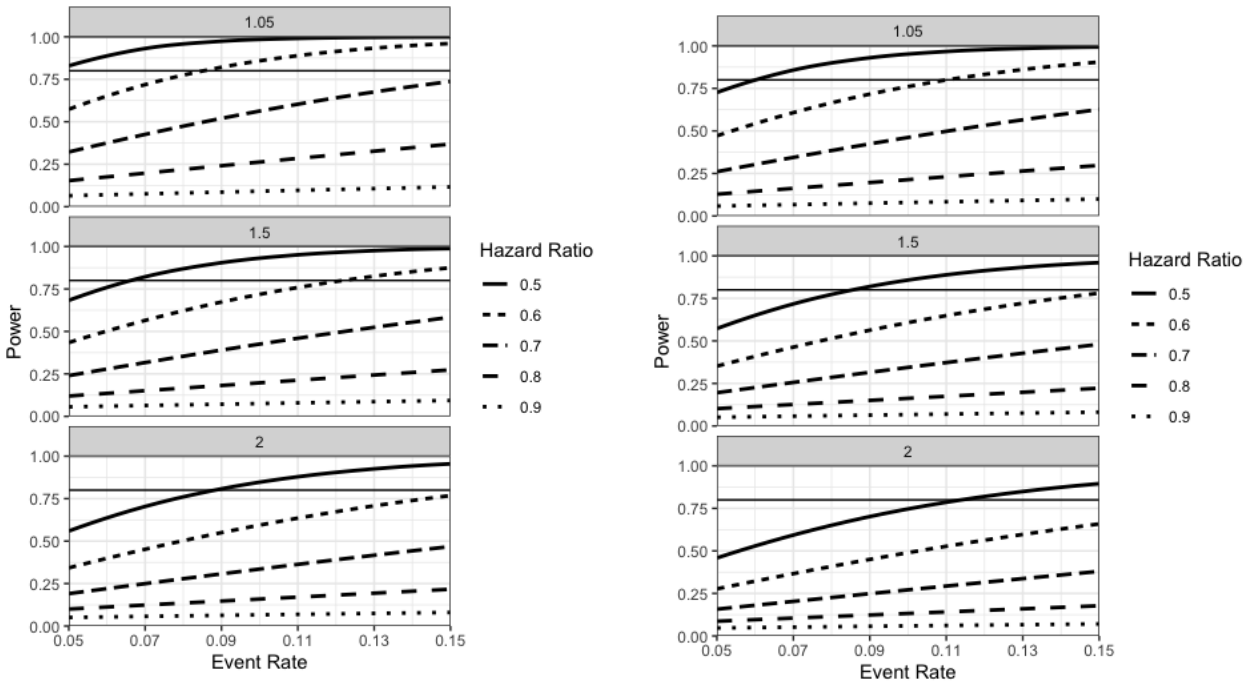
Using the sample size in the 2 populations (Section 6.2), the Sponsor computed power to detect treatment effects (relative hazards) of varying sizes, estimated using Cox proportional hazards regression. Computations are based on the formulae of Schoenfeld 1983. To account for confounding control due to the application of IP weights, the Sponsor inflated the variance from the Schoenfeld formula using factors derived by Shook-Sa 2020. It was conservatively assumed just one control observation per patient. In the Komodo Health data, a preliminary investigation found that approximately 395 patients who meet entry criteria will initiate OCA and that 5916 patients will contribute at least one record to the control group (UDCA nonresponders). In the Global PBC registry, the Sponsor expects to have 344 patients meeting entry criteria who initiate OCA, and 2200 who contribute at least one observation to the control group. Power in both cohorts was computed for relative hazards ranging from 0.5 to 0.9 with an alpha level of 0.05. The Sponsor considered baseline event rates during follow-up from 5% to 15% and variance inflation corresponding to mild confounding (VIF=1.05), moderate confounding (VIF=1.5), and strong confounding (VIF=2.0). In each study, power was plotted under these assumptions against a reference line of 80% power under moderate confounding (VIF=1.5) (Figure 2).

Under mild confounding, both studies will be well-powered to detect an HR of 0.5. For moderate confounding, the Komodo Health study will be adequately powered to detect HR of 0.5 for event rates >6%. The Global PBC registry will be adequately powered to detect event rates >8%. Under strong confounding, the Komodo Health study will be adequately powered to detect

HR of 0.5 for event rates >9%. The Global PBC registry will be adequately powered to detect event rates >11%. Power decreases for more moderate HRs. None of the studies under even the most favorable assumptions will be able to detect HRs of 0.9. The Sponsor notes that the assumptions made here are conservative; in particular, it is expected that many more than one control observation and that the addition of lab data from LabCorp (as noted in Section 6.2) will substantially increase the size of both groups in the Komodo Health study.

Figure 2: Power estimates by Hazard Ratio by Level of Confounding for Komodo Health (A) and Global PBC Registry (B).

A **B**



10.5. Primary Efficacy Analysis

Standard error estimation will proceed using the nonparametric cluster bootstrap (Davison 2013) as has been suggested for nested trial designs using Cox proportional hazards regression (Gran 2010). The standard error will be used to calculate the 95% CI of the hazard ratio and to conduct statistical hypothesis testing. A total of 1000 bootstrap replicates will be used. Bootstrap sampling will occur at the patient level, rather than the patient index level, thus preserving the covariance structure between patient indices and properly accounting for variance inflation due to the covariance between analytic units. Within each bootstrap replicate, all aspects of estimation will be repeated, including the fitting of the treatment model, the construction of the weights, and the fitting of the weighted Cox proportional hazards model used to estimate the treatment effect. The standard deviation of the bootstrap estimates of the treatment effect will be used as an estimate of the standard error. A Wald test will then be conducted using the bootstrap standard error (Cameron 2008). The test statistic is defined as

$w = \frac{\hat{\beta}}{s_{\hat{\beta}}}$, where $\hat{\beta}$ is the estimated coefficient of OCA treatment from the fitted Cox model and $s_{\hat{\beta}}$ is the bootstrap standard error of the estimated coefficient. With a sufficient sample size, w will follow a standard normal distribution and the p-value will be computed as the probability of a normal random variable being greater than $|w|$ or less than $-|w|$. A p-value less than 0.05 will be considered statistically significant.

10.6. Exploratory Analyses

Each component of the study endpoint (all-cause death, liver transplant, and hospitalization for hepatic decompensation) will be assessed separately. For the outcome of death, the analysis will proceed using the same approach as for the primary effect size estimation. For the outcome of liver transplant, death will be treated as a competing event. Here, follow-up will end at the earliest of the end of follow-up, liver transplant, death, or censoring. The analysis will proceed as previously described, but instead of a Cox proportional hazards model, a Fine-Gray proportional subdistribution hazards model will be used (Fine 1999). Similarly, for the outcome of hospitalization for hepatic decompensation, death and liver transplant will be treated as competing events.

10.7. Handling of Dropouts or Missing Data

Patients who disenroll from the covered health plans in Komodo Health or from the Global PBC registry are right-censored at time of disenrollment.

Dropout / disenrollment will be assumed to be uninformative conditional on the included baseline covariates in the Cox model (see Section 10.2). Missing baseline data will be assumed missing completely at random, and a complete case analysis (listwise deletion) will be conducted. During the conduct of the studies, the CRC may recommend refining the missing data strategy to better address any observed pattern of missing data.

10.8. Subgroup Analyses

The entire analysis will be repeated separately by patient race (Komodo Health only), age (categorical), sex, region, absence/presence of cirrhosis, and pre-/post-COVID. Because race is not completely captured in Komodo Health, these analyses will only include those with non-missing values for race.

10.9. Sensitivity Analyses

A quantitative bias analysis will be used to assess the sensitivity of the estimates to violations of the assumption of no unmeasured confounding. To conduct this analysis, it will be assumed that the hazard ratio is a reasonable approximation of the odds ratio, and then previously published formulas for the relation of unadjusted or partially adjusted to adjusted odds ratios will be used to estimate the effect, given inputs for the strength of the confounder treatment and confounder outcome relationships (Lash 2021). The analysis will be conducted across a range of values for the input parameters to assess how much the effect changes given different confounder relationships. Specifically, given the (adjusted for known confounders) odds ratio for the association between the unmeasured confounder and the outcome (OR_{DZ}) and the prevalence of the confounder among the OCA-treated (P_{Z1}) and non-OCA-treated (P_{Z0}) (each assumed

homogeneous across levels of known confounders), the relationship between the partially adjusted and fully adjusted odds ratios is $\frac{OR_{partial}}{OR_{full}} = \frac{OR_{DZ}P_{Z_1}+1-P_{Z_1}}{OR_{DZ}P_{Z0}+1-P_{Z0}}$.

10.10. Assessment of Claims-based PBC Definition

The Komodo Health data are claims-based. Per AASLD guidelines, PBC diagnosis is based on the presence of ≥2 of 3 diagnostic factors:

- History of elevated ALP levels for at least 6 months
- Positive AMA titer
- Liver biopsy finding consistent with PBC

AMA is normally assessed once to diagnose PBC, and the test may have occurred years prior to entry into the Komodo Health claims database. Indeed, a preliminary analysis shows that ~10% of patients with a PBC diagnostic code have an AMA test result in the database. As AMA cannot be used in the definition of PBC, a claims-based analysis will be used to identify PBC patients in claims data requiring 2 outpatient claims or 1 inpatient claim based upon the work of Meyers (Meyers 2010).

Using Canadian ambulatory care and inpatient records, Meyers found that a 2-outpatient claim algorithm had 89% positive predictive value (PPV) when compared to AMA-verified definite, probable, or suspected PBC. A single inpatient claim had 81% PPV, with limited incremental benefit of 2 claims (86% PPV).

In these studies, in addition to the claims criteria, evidence of UDCA use is required, which the Sponsor believes will further improve the PPV of the claims-based algorithm. To validate this approach, the Sponsor will conduct sensitivity and specificity analyses using AMA as the gold standard of PBC diagnosis within the Komodo Health database. The subpopulation of patients with AMA test results (positive vs negative) will be compared to those with a positive and negative diagnosis by the claims + UDCA definition. The sensitivity of the non–AMA-based definition will be defined as the proportion of patients classified as having PBC with the gold standard definition who are also classified as having PBC with the non–AMA-based definition. The negative predictive value of the non–AMA-based definition will be defined as the proportion of patients not classified as having PBC with the non–AMA-based definition who are also not classified as having PBC with the gold standard definition. The specificity and PPV will be assumed to be equal to 1, as the non–AMA-based definition will capture a subset of those individuals classified as having PBC by the gold standard definition.

10.11. Clean Room Committee

In studies of existing data, decisions about study design or analysis should not be informed by knowledge of how such decisions might affect study results. The study team has attempted to pre-specify all statistical analysis plans to a sufficient degree of detail that ambiguity about how the results will be obtained is minimized. However, often data will need to be examined to inform key aspects of the study design or analysis, and in other cases, issues discovered during analysis might require certain deviations from the planned design and/or analysis.

To avoid biasing point estimates and standard errors for the primary comparative analysis, the individuals making these decisions will be isolated from knowledge about how these decisions might affect outcomes. To do this, the 3 individuals will be designated to be members of the CRC, and this designation will be recorded in the study log. Analysts will have direct access to the data and will build all analytic files and implement all data analysis. Study team members not designated as CRC members will work with the analysts to review and understand output tables.

Members of the CRC will make all decisions about the conduct of these studies, including decisions about protocol deviations as well as the reporting and interpretation of results in reports. Additionally, based on data supplied to them by the analysts, the CRC will make decisions about changes in analytic approaches, model specification, group inclusion/exclusion criteria, and variable definitions. The data supplied by the analyst should not provide any direct information about how such protocol changes might affect results. To accomplish this, preliminary results that contain outcome statistics summarized by group (OCA-treated versus not OCA-treated) will not be presented to the Investigators. If, for some reason, results need to be presented by group, the group will be masked by the analysts. All aspects of this process will be tracked, specifically:

- All requests for interim data or results will be entered into the study log where they can be viewed by all study team members.
- All protocol deviations will be logged along with the rationale for the change. Protocol changes will not be made unless all Investigators agree to the change.
- Minutes of meetings in which decisions about protocol changes are made will be saved.
- The original protocol as well as all modified versions will be accessible to all Investigators and analysts.

The original protocol and the study log will be made available as appendix material for all reports and publications.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data in these studies are de-identified. The Komodo Health data use agreements and the Global PBC registry Institutional Review Board (IRB) approval specify that these data may not be re-identified. In addition, the Global PBC registry site agreements do not allow for the transfer of data outside of the Global PBC registry.

The Clinical Research Organization (CRO) will ensure the Investigator's understanding of all applicable regulations and standard operating procedures (SOPs) and will ensure an understanding of the protocol and maintenance of all requisite documentation. The CRO will have full access to the Komodo Health data and analyses to be able to ensure these studies are conducted per protocol. The CRO can also review data and programming on site with a member of the Global PBC Study Group.

A Study Data Tabulation Model (SDTM) dataset will be provided to the FDA for the Komodo Health dataset. Should the FDA have questions or queries, a member of the Global PBC Study

Group will make themselves available on site at the FDA with a laptop computer containing the Global PBC registry analytic dataset and can both review data and run queries as required by the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In 2021, the FDA released 4 draft guidance documents defining data quality, management, and analyses of real-world data, including guidance specific to claims data and disease registries. Given the extensive documentation requirements, separate supplemental protocols will be submitted, one for the Global PBC registry and one for the Komodo Health dataset.

12.1. Data Collection and Transfer

12.1.1. Komodo Health

Komodo Health merges administrative claims across >350 health plans including commercial (63%); Medicaid (23%); Medicare (10%); dual eligible (<1%); and other (2%). The dataset represents more than 325 million unique patients in the US between June 2015 and July 2021. The datasets include all inpatient, outpatient, and procedure claims, as well as service dates, associated ICD-9 and ICD-10 codes, and provider data.

Data from each payer are tokenized, deidentified, and encrypted by the individual payer (see Section 12.2.2). Some examples of file formats Komodo Health intakes from sources include TXT, CSV, and DAT file types. Komodo Health commonly receives data as (but not limited to) comma-delimited, pipe-delimited, and tab-delimited files. A transit token specific to the payer and Komodo Health is used, and once received the data are de-encrypted, including a final patient token. Thirty-six percent of plans transfer their data through a Komodo Health secure FTP site; 64% of plans provide a secure FTP site to Komodo Health to retrieve the data. Komodo Health receives and stores data in AWS S3 buckets.

Plans provide uncurated (raw) data. Data cleaning, such as deduplication, will be specified in the supplemental submission. Cleaned data are merged and linked via token, thus patients are able to be followed longitudinally across plans that contribute data. After Komodo Health finishes processing the data, they are made available as a Snowflake database in the Sentinel cloud environment.

12.1.2. Global PBC Registry

Data for the Global PBC registry is collected through the CASTOR trial platform. The CASTOR System, which has been employed for registrational trials, includes eCRFs, cloud-based data collection, and download of data in SAS format for analysis. The data are only transferred to the University Health Network system, with no additional data transfer, and are analyzed in the SAS environment. The eCRF prevents the input of test values outside of medically plausible range and the input of duplicate data. Source data cannot be modified. The Global PBC registry protocol, eCRFs, and all data cleaning and transformations of variables included in this analysis will be specified in the supplemental submission.

12.1.3. National Death Index

The NDI is a central computerized index of death record information on file in state vital statistics offices. The Centers for Disease Control and Prevention and the National Center for Health Statistics compile deaths annually from computer files submitted by state vital statistics offices. Numerous studies have confirmed the validity of the NDI. The NDI has previously been linked to the Komodo Health database (see Section 12.3) and the datafile will be kept firewalled from analysts until the CRC authorizes unblinding. The NDI will be used to ascertain death as part of the composite endpoint.

The Komodo Health data contains information on hospital discharge status, including death at discharge. Death status, combined with a lack of addition claims >30 days after deaths will be compared to the NDI database. If a death on hospital discharge (plus lack of additional claims) is observed in the Komodo database but not in the NDI database, it will be included as a primary endpoint.

12.1.4. Quest Diagnostics

Quest Diagnostics has >2000 testing facilities with specimens processed at 26 central laboratories in the US (excluding those devoted exclusively to clinical trials). Specimen collection and testing protocols are standardized nationally. Date of test, laboratory value results, normal range limits, and associated ICD-10 codes are entered at each lab facility. Data are sent electronically to the testing site, and also to a centralized main frame and entered into the national database within 7 days. Specifications on data storage, transfer, and cleaning will be included in a supplemental submission.

These studies will utilize ALP, TB, ALT, AST, and platelets to propensity weight treated and untreated patients at index, and to determine UDCA treatment failure. AMA data will be used to validate the ICD-10 PBC claims diagnostic criteria.

12.1.5. LabCorp

LabCorp has >2100 testing facilities with specimens processed at 15 primary laboratories in the US (excluding specialty testing facilities such as oncology and genetic testing). Specimen collection and testing protocols are standardized nationally. Date of test, lab value results, normal range limits, and associated ICD-10 codes are entered at each lab facility. Data are sent electronically to the testing site, and also to a centralized main frame and entered into the national database. Specifications on data storage, transfer, and cleaning will be included in a supplemental submission.

These studies will utilize ALP, TB, ALT, AST, and platelets to propensity weight treated and untreated patients at index, and to determine UDCA treatment failure. AMA data will be used to validate the ICD-10 PBC claims diagnostic criteria.

12.1.6. OPTN Transplant Registry

OPTN collects and reports data on every US organ donor, transplant candidate, recipient, and outcome. Data are collected through a standardized eCRF using the online UNet database system. Specifications on data storage, transfer, and cleaning will be included in a supplemental submission.

The OPTN registry will be the primary data source to ascertain liver transplant as part of the composite endpoint. The Komodo Health data contains information on hospital admissions, including codes for liver transplant (see Appendix A). Hospitalization for liver transplant in Komodo Health claims will be compared to the OPTN database. If a liver transplant is recorded on hospital discharge but not in the OPTN database, it will be included as a primary endpoint.

12.2. Data De-identification

12.2.1. Global PBC Registry

The data collected at each site are de-identified by removing all identifying data fields (name, address, date of birth, etc.) prior to being sent to the Central Coordinating Site. A unique Global PBC Study Group study number is assigned to each site and each participant within the site and does not utilize identifying information in creating the patient number. Identifiers and their relation to the Global PBC Study Group number are maintained only at the study site and not by the central Data Coordinating Site.

12.2.2. Komodo Health

Datavant's de-identification engine is designed for use on structured healthcare data. The de-identification program performs 2 functions: de-identification of the data set through removal or modification of identifying data, and the insertion of encrypted patient tokens.
De-identification includes the following:

- Zip Code: Reduced to the initial three characters to define a zip area. Based on the Health Insurance Portability and Accountability Act (HIPAA) rules, however, even three-digit zip areas with a combined population of less than 20,000 are either nulled out or are combined again with additional zip zones to ensure that populations exceed this minimum.
- Date of Service: Dates of service (eg, admission dates, discharge dates, prescription fill dates, and procedure dates) are typically preserved when using a statistical de-identification methodology.
- Date of Birth: Converts all birth dates to birth year. All dates of birth where the individual aged ≥89 years as of the date of de-identification would be modified to reflect an age of 89.
- Medical Records Numbers: Removed where present
- Telephone Numbers: Removed where present
- Email Address: Removed where present
- Social Security Numbers: Removed where present
- Beneficiary Numbers: Removed where present
- Vehicle Information: Removed where present
- Device Identifiers and Serial Numbers: Removed where present
- URL Addresses: Removed where present

- IP Addresses: Removed where present
- Biometric Values: Removed where present in claims data; retained in Quest Diagnostics and LabCorp
- Image Fields: Removed as defined by the data source

Datavant does not perform de-identification and tokenization itself and does not have access to the user's system or identifying information. The de-identification process is executed by the institution that owns the data, ie, Datavant's technology is installed and run locally behind the users' firewalls.

12.3. Data Linkages

Two sets of linkages are relevant for Komodo Health: initial link of contributing administrative claims databases; and linkage of laboratory data (LabCorp and Quest Diagnostics), death date (NDI), and transplant date (OPTN registry). All data linkages will be done through Datavant tokenization.

Across all datasets, as the Datavant program de-identifies a patient record, it also generates one or more tokens for that record. Tokens are based on the personally identifying data in the record, but the token itself does not incorporate this information in the identifier. The tokens are consistently created from any data set where the underlying identifying information is the same. Matching tokens are used to link a patient's record in one data set with a record for the same patient in a different set, without exposing the identifying information of that patient. Matching can be deterministic (eg, based on social security number) or probabilistic (eg, based on combination or name, sex, birthdate, 3-digit zip code, etc).

The tokens used to link records in de-identified data sets cannot be reversed to reveal the patient's identifying information. The first step of the token creation process is the use of an irreversible hash function, which ensures that the patient's personally identifying information used to create the token cannot be recovered from the output value. In the second step of the process, the hash value (ie, "Master Token") is encrypted with a site-specific encryption key to generate the final encrypted patient token. While the same patient information will always create the same Master Token, site-specific encryption means that a single patient will have a unique token (ie, a "site-specific token") in each specific user's data set. Site-specific encryption ensures that a breach at one data site will never compromise the tokens or protected health information at any other data site. Datavant's QA testing protocols and results will be included in the supplementary submission.

Across all datasets, Datavant will create 2 tokens based on:

- Last name + first name + gender + date of birth
- Last name (soundex) + first name (soundex) + gender + date of birth

In the event this produces 2 patients with one token (called a "collision") or one patient with 2 tokens, Datavant will then match on social security number and/or address (when available in the dataset). In the overall Komodo Health claims database, in the match with the NDI, and in the match with Quest Diagnostics data, this has produced 99% exact match. In the subset of

PBC patients, only 873 of 164,942 patients are flagged as a collision and have been removed from analysis. The same process will be used with the OPTN transplant data.

12.4. Data Harmonization

The Global PBC registry collects data via a standardized eCRF. As such, data harmonization across data sources is not required.

The Komodo Health database merges administrative claims data from multiple insurers in the US. Claims are then merged with NDI for date of death; LabCorp and Quest Diagnostics databases for laboratory tests and values; and OPTN transplant registry for date of liver transplant. Below are the data sources and variables for which data harmonization is required and performed.

12.4.1. Komodo Health and National Death Index

The primary endpoint is a composite of all-cause death, liver transplant, and hospitalization for hepatic decompensation. The primary source for death will be the NDI. The Komodo Health claims database contains hospital discharge status, including "death." Hospital discharge of death will be compared to the NDI. Should a death be recorded on hospital discharge but not in the NDI, and if the patient has no healthcare claims 30 days after the "death" discharge, the patient will be coded as a death using the hospital discharge date.

12.4.2. Komodo Health and OPTN Liver Transplant

The primary endpoint is a composite of all-cause death, liver transplant, and hospitalization for hepatic decompensation. The primary source for liver transplant will be the OPTN transplant registry. Hospitalization for liver transplant in Komodo Health claims also will be ascertained through inpatient ICD-10 codes (see Section 12.4.3 and Appendix A). Komodo Health liver transplant claims will be compared to the OPTN database. Should a liver transplant be recorded for a hospitalization but not in the OPTN database, it will be included as a primary endpoint.

12.4.3. Komodo Health Hospitalization for Hepatic Decompensation

The primary endpoint is a composite of all-cause death, liver transplant, and hospitalization for hepatic decompensation. The primary source for hospitalization for hepatic decompensation will be Komodo Health claims. The definition will include inpatient admission ICD-10 codes that appear in any position, and includes:

- Variceal bleed: ICD-10: I85.01, I85.11, I86.4 and ICD-9: 456.1, 456.21, 456.8
- Ascites: ICD-10: K70.11, K70.31, K71.51, R18.0, R18.8, J94.8, K65.2 and ICD-9: 567.23, 571.2, 789.51,789.59, 511.8, 567.23
- Hepatic encephalopathy: ICD-10: B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, K70.41, K72.11, K72.90, K72.91 and ICD-9: 572.2, 070.0, 070.20, 070.41, 070.6, 070.71; or utilization of lactulose and/or rifaximin

As ICD-10 codes are standard across the US healthcare industry, there is no need for further harmonization across contributing health plans.

12.4.4. Quest Diagnostics and LabCorp

Within each laboratory provider, sample collection, test, and normal ranges are standardized. Collection and transport specifications, laboratory method, and normal ranges for each test are provided by each lab below.

- Total bilirubin (test code: Quest 285, LabCorp 001099)
  - Quest Diagnostics: Samples are collected in sodium heparin (green-top) or lithium heparin (green-top) tubes, spun in a serum separator tube, transported in a serum separator tube wrapped in foil or transferred to an amber transport vial, and stored/transported at room temperature with stability up to 24 hours. Spectrophotometry is performed on 1 mL serum. ULN is 1.2 mg/dL.
  - LabCorp: Samples are collected in red top gel-barrier tube or lithium heparin (green-top) tubes, with serum separation in ≤45 minutes, and stored/transported at room temperature with stability up to 3 days. Spectrophotometry testing is performed on 1 mL serum. ULN is 1.2 mg/dL for ≥18-year-olds.
- Alkaline phosphatase (test code: Quest 234, LabCorp 001107)
  - Quest Diagnostics: Samples are collected in sodium heparin (green-top) or lithium heparin (green-top) tubes, spun and transported in a serum separator tube, and stored/transported at room temperature with stability up to 7 days. Spectrophotometry is performed on 1 mL serum. ULN in U/L for 18- to 19-year-olds is 169 for men and 128 for women; for 20- to 49-year-olds is 130 for men and 125 for women; and for ≥50-year-olds 144 for men and 153 for women.
  - LabCorp: Samples are collected in red top gel-barrier tube or lithium heparin (green-top) tubes, with serum separation in ≤45 minutes, and 1 mL serum transported in plastic separator tube, and stored/transported at room temperature with stability up to 14 days. Kinetic testing is performed on 1 mL serum. ULN in IU/L for 18- to 20-year-olds is 125 for men and 106 for women; for ≥21-year-olds is 121 for men and women.
- Alanine aminotransferase (test code: Quest 823, LabCorp 001545)
  - Quest: Samples are collected in sodium heparin (green-top) or lithium heparin (green-top) tubes, spun and transported in a serum separator tube, and stored/transported at room temperature with stability up to 72 hours. Spectrophotometry is performed on 1 mL serum. ULN in U/L for 18- to 19-year-olds is 46 for men and 32 for women; for ≥20-year-olds is 46 for men and 29 for women.
  - LabCorp: Samples are collected in red top gel-barrier tube or lithium heparin (green-top) tubes, with serum separation in ≤45 minutes, and stored/transported at room temperature with stability up to 7 days. Kinetic testing is performed on 1 mL serum. ULN is 44 IU/L for ≥18-year-olds.

- Aspartate Aminotransferase (test code: Quest 822, LabCorp 001123)
  - Quest Diagnostics: Samples are collected in sodium heparin (green-top) or lithium heparin (green-top) tubes, spun and transported in a serum separator tube, and stored/transported at room temperature with stability up to 4 days. Spectrophotometry is performed on 1 mL serum. ULN in U/L for 18- to 19-year-old men and women is 32; for men, 20- to 49-year-olds is 40 and ≥50-year-olds is 35; for women, 20- to 44-year olds is 30 and ≥45-year-olds is 35.
  - LabCorp: Samples are collected in red top gel-barrier tube or lithium heparin (green-top) tubes, with serum separation in ≤45 minutes, and stored/transported at room temperature with stability up to 7 days. Kinetic testing is performed on 1 mL serum. ULN is 40 IU/L for ≥18-year-olds.
- Platelets (test code: Quest 723, LabCorp 005249)
  - Quest Diagnostics: Samples are collected in lavender-top (EDTA) tubes and stored/transported at room temperature with stability up to 48 hours. Testing is performed on 0.5 mL whole blood using an automated cell counter. Lower limit of normal (LLN) is 150,000 per uL for ≥18-year-olds.
  - LabCorp: Samples are collected in lavender-top (EDTA) tubes, immediately inverted 8 to 10 times, and stored/transported at room temperature with stability up to 1 day. Testing is performed on 0.5 mL whole blood using an automated cell counter. LLN is 150,000 per uL for ≥18-year-olds.

12.4.5. Cirrhosis

In the Global PBC registry, cirrhosis is assessed as positive for one or more of the following criteria:

- Biopsy Stage 4;
- Transient elastography ≥16.9 kPa;
- Radiological evidence (nodular liver or enlargement of portal vein + splenomegaly);
- Clinical features of portal hypertension defined as platelet count <140 000/mm³ with: persistent decrease in serum albumin; or, TB >2x ULN; or prothrombin time/INR > ULN (not due to antithrombotic use)

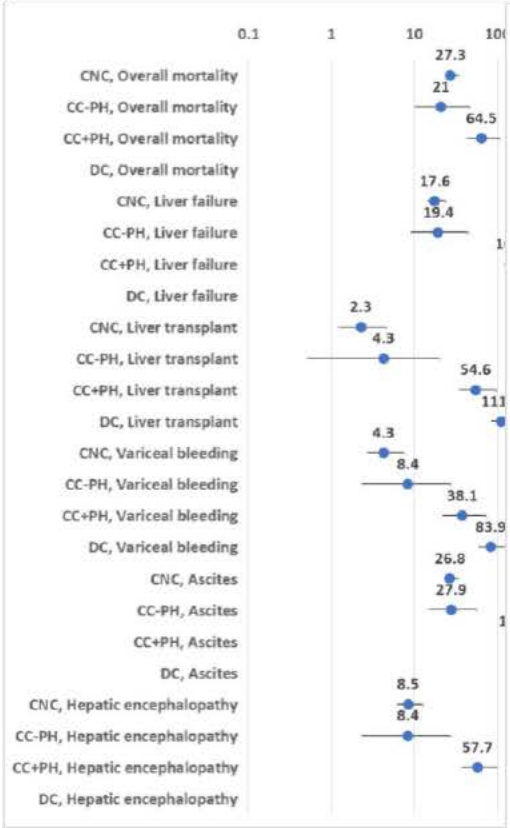
In the Komodo Health database, imaging data are not available and measures such as INR are not consistently collected. The Sponsor created and validated an algorithm for a claims-based cirrhosis diagnosis, defined as: cirrhosis ICD-10 (K74.5; K74.60; K74.69) with liver imaging and/or biopsy in 6 months preceding diagnosis (for imaging codes see Appendix A). Prevalence estimates in patients with PBC based on these codes in the HealthCore and Optum databases, stratified by decompensation and portal hypertension, were compared to data from the Global PBC registry (Table 2). As shown, the concordance was high. Additional analyses examining the association between these groups and clinical outcomes (death, liver transplant and hepatic decompensation) demonstrated that the expected relationships, with cirrhosis in the presence of portal hypertension or decompensation significantly increasing risk of death, liver failure and liver transplantation (Figure 3).

Table 2: Comparison of Imaging-based (Global PBC) and Claims-based (HealthCore, Optum) Prevalence of Cirrhosis in PBC Patients.

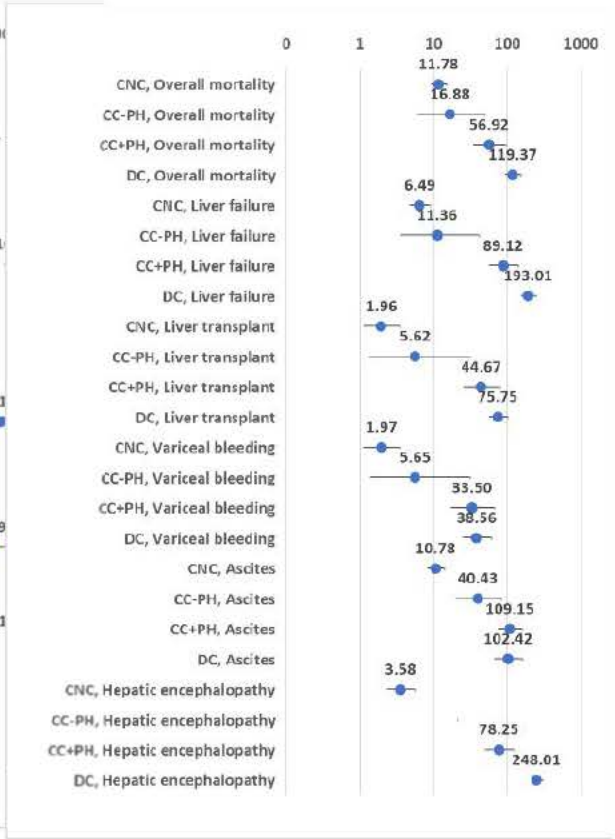
	Global PBC	Optum	HealthCore
PBC	N=2,982 (100%)	N=4,328 (100%)	N=4,348 (100%)
Compensated non-cirrhosis	N=2,275 (76.3%)	N=3,303 (76.3%)	N=3,317 (76.3%)
Compensated cirrhosis, without portal hypertension	N=314 (10.5%)	N=271 (6.3%)	N=225 (5.2%)
Compensated cirrhosis, with portal hypertension	N=105 (3.5%)	N= 276 (6.4%)	N=295 (6.8%)
Decompensated	N=283 (9.5%)	N=478 (11.0%)	N=511 (11.8%)

Figure 3: Incidence Rates for Major Hepatic Events Stratified by Cirrhosis, Portal Hypertension and Hepatic Decompensation in the Optum (A) and HealthCore (B) Databases

A. Optum



B. HealthCore



12.5. Characterization of Missing Data

Missing data will be assumed to be missing at random. As per FDA draft real-world evidence (RWE) guidelines, missing data are characterized by year (see Appendix B) and will undertake an analysis of secular trend to determine if missingness varies by time. Should secular trends exist, the CRC will determine the best approach to addressing bias, and that approach will be included in a protocol revision.

12.6. Data Management and Analysis SOPs

The FDA draft guidance on RWE requires a data management plan as well as copies of all relevant data management and analysis SOPs. These will be included in a supplemental submission and defined separately for the Global PBC study group and the CRO analyzing the Komodo data.

12.7. Audits and Inspections

The Investigators should understand that it may be necessary for the Sponsor, the IRB/Independent Ethics Committee (IEC), and/or regulatory agencies to conduct one or more site audits during or after the study and agree to allow access to all study-related documentation and information and be available for discussion about the study.

12.8. Quality Control and Quality Assurance

Logic and consistency checks will be performed on all data in the database to ensure accuracy and completeness. SOPs from the CRO analyzing the Komodo data and the Global PBC Study Group governing data management and analysis will be provided in a supplemental submission.

Given the short length of the study conduct period (approximately 6 months for analysis and clinical study report), the Sponsor will conduct a single monitoring visit at each site. Study records will be reviewed to ensure maintenance and documentation of complete, accurate, legible, well-organized, and easily retrievable data. The Sponsor will ensure the Investigator's understanding of the protocol, reporting responsibilities, and the validity of the data. This will include ensuring that full and appropriate essential documentation is available. To perform analytic file and analysis verification, the Sponsor must be given access to the analytic file, SAS code and code annotation. The Sponsor will not alter data or programming, nor will transport any data from the site.

12.9. Data Retention and Archiving Study Documents

The CRO analyzing the Komodo data and the Global PBC Study Group will retain the data and all study documents after delivery of the project for a maximum period as required by the applicable regulatory requirement(s) or the Sponsor. In the event that storage of data becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the CRO and the Global PBC Study Group should obtain written authorization from the Sponsor before the destruction of any records. The Sponsor will inform the CRO and the Global PBC Study Group should it become aware of any changes in storage requirements.

13. PROTECTION OF HUMAN SUBJECTS

These studies will be conducted in accordance with HIPAA regulations and US standards of privacy of individually identifiable health information.

The Global PBC registry was approved by the University Health Network IRB at the University of Toronto (CAPCR ID: 19-5678).

All data used in these studies are anonymized, and analyses will be performed on de-identified patient-level datasets. While patient data will be anonymized and the studies are observational and retrospective in nature and thus would qualify for exemption under the Common Rule, these studies are being submitted to Western IRB for full review.

The data system will be maintained and secured as requested by the US patient privacy regulations. Processes assuring data security will be employed during data extraction, storage, and backup. The data and all study documents will be kept until the Sponsor's written notification that records may be destroyed.

14. ADVERSE EVENT REPORTING

As stated in Section 9 (Assessment of Safety), these studies are not designed to assess safety. Study outcome variables collected for the 2 cohorts will be presented for analyses as aggregate data groups. The data sources will not be searched for individual patient adverse events. However, if an Investigator or the Sponsor identifies adverse events that meet postmarketing reporting requirements during the course of conducting these studies, such events will be reported in accordance with applicable postmarketing reporting requirements.

15. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the studies that it sponsors, regardless of outcome and consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators, and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for studies that are appropriate for these studies. Key issues include the following:

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of these studies and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers, and editors will have the right to audit the data to verify its accuracy.

- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Intercept Review of External Manuscripts: Investigators must submit any drafts of any publications or presentations that may arise from these studies to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies, or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit; eg, protocol and amendments and data tabulations. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

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APPENDIX A. LIST OF INCLUSION, EXCLUSION AND COVARIATE CODES

INCLUSION/EXCLUSION CRITERIA CODES

CODE	TYPE	DESCRIPTION
Inclusion criteria		
K74.3	ICD10	Primary biliary cholangitis
571.6	ICD9	Biliary cirrhosis (for rule-out in the baseline period)
Exclusion criteria		
0FY00Z1	ICD10 pcs	Transplantation of liver, syngeneic, open approach
0FY00Z0	ICD10 pcs	Transplantation of Liver, Allogeneic, Open Approach
47135	HCPCS/ CPT-4	Liver allotransplantation; orthotopic; partial or whole, from cadaver or living donor, any age
B17.10	ICD10	Acute hepatitis C without hepatic coma
B17.11	ICD10	Acute hepatitis C with hepatic coma
070.41	ICD9	Acute hepatitis C with hepatic coma
070.51	ICD9	Acute hepatitis C without mention of hepatic coma
B18.2	ICD10	Chronic viral hepatitis C
070.44	ICD9	Chronic hepatitis C with hepatic coma
070.54	ICD9	Chronic hepatitis C without mention of hepatic coma
070.70	ICD9	Unspecified viral hepatitis C without hepatic coma
070.71	ICD9	Unspecified viral hepatitis C with hepatic coma
B16.0	ICD10	Acute hepatitis B with delta-agent with hepatic coma
B16.1	ICD10	Acute hepatitis B with delta-agent without hepatic coma
B16.2	ICD10	Acute hepatitis B without delta-agent with hepatic coma
B16.9	ICD10	Acute hepatitis B without delta-agent and without hepatic coma
B17.0	ICD10	Acute delta-(super) infection of hepatitis B carrier
070.20	ICD9	Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta
070.21	ICD9	Viral hepatitis B with hepatic coma, acute or unspecified, with hepatitis delta
070.30	ICD9	Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta
070.31	ICD9	Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta
B18.0	ICD10	Chronic viral hepatitis B with delta-agent
B18.1	ICD10	Chronic viral hepatitis B without delta-agent
070.23	ICD9	Chronic viral hepatitis B with hepatic coma with hepatitis delta
070.22	ICD9	Chronic viral hepatitis B with hepatic coma without hepatitis delta
070.33	ICD9	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
070.32	ICD9	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
K83.01	ICD10	Primary sclerosing cholangitis (2019-2021 only)
K70.0	ICD10	Alcoholic fatty liver

CODE	TYPE	DESCRIPTION
K70.10	ICD10	Alcoholic hepatitis without ascites
K70.11	ICD10	Alcoholic hepatitis with ascites
K70.2	ICD10	Alcoholic fibrosis and sclerosis of liver
K70.30	ICD10	Alcoholic cirrhosis of liver without ascites
K70.31	ICD10	Alcoholic cirrhosis of liver with ascites
K70.40	ICD10	Alcoholic hepatic failure without coma
K70.41	ICD10	Alcoholic hepatic failure with coma
K70.9	ICD10	Alcoholic liver disease, unspecified
571.0	ICD9	Alcoholic fatty liver
571.1	ICD9	Acute alcoholic hepatitis
571.2	ICD9	Alcoholic cirrhosis of liver
571.3	ICD9	Alcoholic liver damage, unspecified
C22.0	ICD10	Liver cell carcinoma
C22.8	ICD10	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	ICD10	Malignant neoplasm of liver, not specified as primary or secondary
155.0	ICD9	Malignant neoplasm of liver, primary
155.2	ICD9	Malignant neoplasm of liver, not specified as primary or secondary
K76.7	ICD10	Hepatorenal syndrome
572.4	ICD9	Hepatorenal syndrome
K76.81	ICD10	Hepatopulmonary syndrome
573.5	ICD9	Hepatopulmonary syndrome
I27.21	ICD10	Secondary pulmonary arterial hypertension
K75.81	ICD10	Nonalcoholic steatohepatitis
571.8	ICD9	Other chronic nonalcoholic liver disease
C00	ICD10	Malignant neoplasm of lip
C02	ICD10	Malignant neoplasm of other and unspecified parts of tongue
C03	ICD10	Malignant neoplasm of gum
C04	ICD10	Malignant neoplasm of floor of mouth
C05	ICD10	Malignant neoplasm of palate
C06	ICD10	Malignant neoplasm of other and unspecified parts of mouth
C08	ICD10	Malignant neoplasm of other and unspecified major salivary glands
C09	ICD10	Malignant neoplasm of tonsil
C10	ICD10	Malignant neoplasm of oropharynx
C11	ICD10	Malignant neoplasm of nasopharynx
C13	ICD10	Malignant neoplasm of hypopharynx
C14	ICD10	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity & pharynx
C15	ICD10	Malignant neoplasm of esophagus
C16	ICD10	Malignant neoplasm of stomach
C17	ICD10	Malignant neoplasm of small intestine
C18	ICD10	Malignant neoplasm of colon
C21	ICD10	Malignant neoplasm of anus and anal canal

CODE	TYPE	DESCRIPTION
C22	ICD10	Malignant neoplasm of liver and intrahepatic bile ducts
C24	ICD10	Malignant neoplasm of other and unspecified parts of biliary tract
C25	ICD10	Malignant neoplasm of pancreas
C26	ICD10	Malignant neoplasm of other and ill-defined digestive organs
C30	ICD10	Malignant neoplasm of nasal cavity and middle ear
C31	ICD10	Malignant neoplasm of accessory sinuses
C32	ICD10	Malignant neoplasm of larynx
C34	ICD10	Malignant neoplasm of bronchus and lung
C38	ICD10	Malignant neoplasm of heart, mediastinum and pleura
C39	ICD10	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40	ICD10	Malignant neoplasm of bone and articular cartilage of limbs
C41	ICD10	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C47	ICD10	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48	ICD10	Malignant neoplasm of retroperitoneum and peritoneum
C49	ICD10	Malignant neoplasm of other connective and soft tissue
C50	ICD10	Malignant neoplasm of breast
C51	ICD10	Malignant neoplasm of vulva
C53	ICD10	Malignant neoplasm of cervix uteri
C54	ICD10	Malignant neoplasm of corpus uteri
C56	ICD10	Malignant neoplasm of ovary
C57	ICD10	Malignant neoplasm of other and unspecified female genital organs
C60	ICD10	Malignant neoplasm of penis
C62	ICD10	Malignant neoplasm of testis
C63	ICD10	Malignant neoplasm of other and unspecified male genital organs
C64	ICD10	Malignant neoplasm of kidney, except renal pelvis
C65	ICD10	Malignant neoplasm of renal pelvis
C66	ICD10	Malignant neoplasm of ureter
C67	ICD10	Malignant neoplasm of bladder
C68	ICD10	Malignant neoplasm of other and unspecified urinary organs
C69	ICD10	Malignant neoplasm of eye and adnexa
C70	ICD10	Malignant neoplasm of meninges
C71	ICD10	Malignant neoplasm of brain
C72	ICD10	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C74	ICD10	Malignant neoplasm of adrenal gland
C75	ICD10	Malignant neoplasm of other endocrine glands and related structures
C76	ICD10	Malignant neoplasm of other and ill-defined sites
C77	ICD10	Secondary and unspecified malignant neoplasm of lymph nodes
C78	ICD10	Secondary malignant neoplasm of respiratory and digestive organs
C79	ICD10	Secondary malignant neoplasm of other and unspecified sites

CODE	TYPE	DESCRIPTION
C80	ICD10	Malignant neoplasm without specification of site
140	ICD9	Malignant neoplasm of lip
141	ICD9	Malignant neoplasm of tongue
142	ICD9	Malignant neoplasm of major salivary glands
143	ICD9	Malignant neoplasm of gum
144	ICD9	Malignant neoplasm of floor of mouth
145	ICD9	Malignant neoplasm of other and unspecified parts of mouth
146	ICD9	Malignant neoplasm of oropharynx
147	ICD9	Malignant neoplasm of nasopharynx
148	ICD9	Malignant neoplasm of hypopharynx
149	ICD9	Malignant neoplasm of other and ill-defined sites within the lip, oral cavity, and pharynx
150	ICD9	Malignant neoplasm of esophagus
151	ICD9	Malignant neoplasm of stomach
152	ICD9	Malignant neoplasm of small intestine, including duodenum
153	ICD9	Malignant neoplasm of colon
154	ICD9	Malignant neoplasm of rectum, rectosigmoid junction, and anus
155	ICD9	Malignant neoplasm of liver and intrahepatic bile ducts
156	ICD9	Malignant neoplasm of gallbladder and extrahepatic bile ducts
157	ICD9	Malignant neoplasm of pancreas
158	ICD9	Malignant neoplasm of retroperitoneum and peritoneum
159	ICD9	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
160	ICD9	Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
161	ICD9	Malignant neoplasm of larynx
162	ICD9	Malignant neoplasm of trachea, bronchus, and lung
163	ICD9	Malignant neoplasm of pleura
164	ICD9	Malignant neoplasm of thymus, heart, and mediastinum
165	ICD9	Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
170	ICD9	Malignant neoplasm of bone and articular cartilage
171	ICD9	Malignant neoplasm of connective and other soft tissue
174	ICD9	Malignant neoplasm of female breast
175	ICD9	Malignant neoplasm of male breast
180	ICD9	Malignant neoplasm of cervix uteri
182	ICD9	Malignant neoplasm of body of uterus
183	ICD9	Malignant neoplasm of ovary and other uterine adnexa
184	ICD9	Malignant neoplasm of other and unspecified female genital organs
186	ICD9	Malignant neoplasm of testis
187	ICD9	Malignant neoplasm of penis and other male genital organs
188	ICD9	Malignant neoplasm of bladder

CODE	TYPE	DESCRIPTION
189	ICD9	Malignant neoplasm of kidney and other and unspecified urinary organs
190	ICD9	Malignant neoplasm of eye
191	ICD9	Malignant neoplasm of brain
192	ICD9	Malignant neoplasm of other and unspecified parts of nervous system
194	ICD9	Malignant neoplasm of other endocrine glands and related structures
195	ICD9	Malignant neoplasm of other and ill-defined sites
196	ICD9	Secondary and unspecified malignant neoplasm of lymph nodes
197	ICD9	Secondary malignant neoplasm of respiratory and digestive systems
198	ICD9	Secondary malignant neoplasm of other specified sites
199	ICD9	Malignant neoplasm without specification of site
B20	ICD10	Human immunodeficiency virus infection
B21	ICD10	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
B22	ICD10	Human immunodeficiency virus [HIV] disease resulting in other specified diseases
042	ICD9	Human immunodeficiency virus [HIV] infection
M88.0	ICD10	Osteitis deformans of skull
M88.1	ICD10	Osteitis deformans of vertebrae
M88.811	ICD10	Osteitis deformans of right shoulder
M88.812	ICD10	Osteitis deformans of left shoulder
M88.819	ICD10	Osteitis deformans of unspecified shoulder
M88.821	ICD10	Osteitis deformans of right upper arm
M88.822	ICD10	Osteitis deformans of left upper arm
M88.829	ICD10	Osteitis deformans of unspecified upper arm
M88.831	ICD10	Osteitis deformans of right forearm
M88.832	ICD10	Osteitis deformans of left forearm
M88.839	ICD10	Osteitis deformans of unspecified forearm
M88.841	ICD10	Osteitis deformans of right hand
M88.842	ICD10	Osteitis deformans of left hand
M88.849	ICD10	Osteitis deformans of unspecified hand
M88.851	ICD10	Osteitis deformans of right thigh
M88.852	ICD10	Osteitis deformans of left thigh
M88.859	ICD10	Osteitis deformans of unspecified thigh
M88.861	ICD10	Osteitis deformans of right lower leg
M88.862	ICD10	Osteitis deformans of left lower leg
M88.869	ICD10	Osteitis deformans of unspecified lower leg
M88.871	ICD10	Osteitis deformans of right ankle and foot
M88.872	ICD10	Osteitis deformans of left ankle and foot
M88.879	ICD10	Osteitis deformans of unspecified ankle and foot
M88.88	ICD10	Osteitis deformans of other bones
M88.89	ICD10	Osteitis deformans of multiple sites
M88.9	ICD10	Osteitis deformans of unspecified bone
731.0	ICD9	Osteitis deformans without mention of bone tumor

CODE	TYPE	DESCRIPTION
S02	ICD10	Fracture of skull and facial bones
S12	ICD10	Fracture of cervical vertebra and other parts of neck
S22	ICD10	Fracture of rib(s), sternum and thoracic spine
S32	ICD10	Fracture of lumbar spine and pelvis
S42	ICD10	Fracture of shoulder and upper arm
S52	ICD10	Fracture of forearm
S62	ICD10	Fracture at wrist and hand level
S72	ICD10	Fracture of femur
S82	ICD10	Fracture of lower leg, including ankle
S92	ICD10	Fracture of foot and toe, except ankle
800	ICD9	Fracture of vault of skull
801	ICD9	Fracture of base of skull
802	ICD9	Fracture of face bones
803	ICD9	Other and unqualified skull fractures
804	ICD9	Multiple fractures involving skull or face with other bones
805	ICD9	Fracture of vertebral column without mention of spinal cord injury
806	ICD9	Fracture of vertebral column with spinal cord injury
807	ICD9	Fracture of rib(s) sternum larynx and trachea
808	ICD9	Fracture of pelvis
809	ICD9	Ill-defined fractures of bones of trunk
810	ICD9	Fracture of clavicle
811	ICD9	Fracture of scapula
812	ICD9	Fracture of humerus
813	ICD9	Fracture of radius and ulna
814	ICD9	Fracture of carpal bone(s)
815	ICD9	Fracture of metacarpal bone(s)
816	ICD9	Fracture of one or more phalanges of hand
817	ICD9	Multiple fractures of hand bones
818	ICD9	Ill-defined fractures of upper limb
819	ICD9	Multiple fractures involving both upper limbs and upper limb with rib(s) and sternum
820	ICD9	Fracture of neck of femur
821	ICD9	Fracture of other and unspecified parts of femur
822	ICD9	Fracture of patella
823	ICD9	Fracture of tibia and fibula
824	ICD9	Fracture of ankle
825	ICD9	Fracture of one or more tarsal and metatarsal bones
826	ICD9	Fracture of one or more phalanges of foot
827	ICD9	Other multiple and ill-defined fractures of lower limb
828	ICD9	Multiple fractures involving both lower limbs lower with upper limb and lower limb(s) with rib(s) and sternum
829	ICD9	Fracture of unspecified bones

CODE	TYPE	DESCRIPTION
I85.01	ICD10	Esophageal varices with bleeding
I85.11	ICD10	Secondary esophageal varices with bleeding
456.0	ICD9	Esophageal varices with bleeding
K70.11	ICD10	Alcoholic hepatitis with ascites
K70.31	ICD10	Alcoholic cirrhosis of liver with ascites
K71.51	ICD10	Toxic liver disease with chronic active hepatitis with ascites
R18.0	ICD10	Malignant ascites
R18.8	ICD10	Other ascites
571.2	ICD9	Alcoholic cirrhosis of liver
789.51	ICD9	Malignant ascites
789.59	ICD9	Other ascites
J94.8	ICD10	Other specified pleural conditions
511.8	ICD9	Other specified forms of pleural effusion, except tuberculous
567.23	ICD9	Spontaneous bacterial peritonitis
K65.2	ICD10	Spontaneous bacterial peritonitis
B15.0	ICD10	Hepatitis A with hepatic coma
B16.0	ICD10	Acute hepatitis B with delta-agent with hepatic coma
B16.2	ICD10	Acute hepatitis B without delta-agent with hepatic coma
B17.11	ICD10	Acute hepatitis C with hepatic coma
B19.0	ICD10	Unspecified viral hepatitis with hepatic coma
B19.11	ICD10	Unspecified viral hepatitis B with hepatic coma
B19.21	ICD10	Unspecified viral hepatitis C with hepatic coma
K70.41	ICD10	Alcoholic hepatic failure with coma
K72.11	ICD10	Chronic hepatic failure with coma
K71.11	ICD10	Toxic liver disease with hepatic necrosis, with coma
K72.01	ICD10	Acute and subacute hepatic failure with coma
K72.91	ICD10	Hepatic failure, unspecified with coma
572.2	ICD9	Hepatic encephalopathy
070.0	ICD9	Viral hepatitis A with hepatic coma
070.21	ICD9	Viral hepatitis B with hepatic coma, acute or unspecified, with hepatitis delta
070.20	ICD9	Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta
070.2	ICD9	Viral hepatitis b with hepatic coma
070.6	ICD9	Unspecified viral hepatitis with hepatic coma
070.4	ICD9	Other specified viral hepatitis with hepatic coma
070.41	ICD9	Acute hepatitis C with hepatic coma
070.6	ICD9	Unspecified viral hepatitis with hepatic coma
070.71	ICD9	Unspecified viral hepatitis C with hepatic coma
Z48.23	ICD10	Encounter for aftercare following liver transplant
V42.7	ICD9	Liver transplant status
T86.40	ICD10	Unspecified complication of liver transplant
T86.41	ICD10	Liver transplant rejection

CODE	TYPE	DESCRIPTION
T86.42	ICD10	Liver transplant failure
T86.43	ICD10	Liver transplant infection
T86.49	ICD10	Other complications of liver transplant
996.82	ICD9	Complications of transplanted liver

COVARIATE CODES (INLCUDING CHARLESON COMORBIDITY INDEX

CODE	TYPE	DESCRIPTION
K76.6	ICD10	Portal hypertension
572.3	ICD9	Portal hypertension
I86.4	ICD10	Gastric varices
456.8	ICD9	Varices of other sites (non-specific)
I85.00	ICD10	Esophageal varices without bleeding
I85.10	ICD10	Secondary esophageal varices without bleeding
456.1	ICD9	Esophageal varices without mention of bleeding
456.21	ICD9	Esophageal varices in diseases classified elsewhere, without mention of bleeding
K74.5	ICD10	Biliary cirrhosis, unspecified
K74.60	ICD10	Unspecified cirrhosis of liver
K74.69	ICD10	Other cirrhosis of liver
571.5	ICD9	Cirrhosis of liver without mention of alcohol
I21	ICD10	Acute myocardial infarction
I22	ICD10	Subsequent ST elevation and non-ST elevation myocardial infarction
I25.2	ICD10	Old myocardial infarction
410	ICD9	Acute myocardial infarction
412	ICD9	Old myocardial infarction
I11.0	ICD10	Hypertensive heart disease with heart failure
I13.0	ICD10	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.2	ICD10	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I25.5	ICD10	Ischemic cardiomyopathy
I42.0	ICD10	Cardiomyopathy
I42.5	ICD10	Other restrictive cardiomyopathy
I42.6	ICD10	Alcoholic cardiomyopathy
I42.7	ICD10	Cardiomyopathy due to drug and external agent
I42.8	ICD10	Other cardiomyopathies
I42.9	ICD10	Cardiomyopathy, unspecified
I43	ICD10	Cardiomyopathy in diseases classified elsewhere
I50	ICD10	Heart failure
P29.0	ICD10	Neonatal cardiac failure
398.91	ICD9	Rheumatic heart failure (congestive)
402.01	ICD9	Malignant hypertensive heart disease with heart failure
402.11	ICD9	Benign hypertensive heart disease with heart failure
402.91	ICD9	Unspecified hypertensive disease with heart failure
404.01	ICD9	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease.
404.03	ICD9	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease

CODE	TYPE	DESCRIPTION
404.11	ICD9	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	ICD9	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	ICD9	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	ICD9	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
425.4	ICD9	Other primary cardiomyopathies
425.5	ICD9	Alcoholic cardiomyopathy
425.6	ICD9	Cardiomyopathy in Chagas disease
425.7	ICD9	Nutritional and metabolic cardiomyopathy
425.8	ICD9	Cardiomyopathy in other disease classified elsewhere
425.9	ICD9	Secondary cardiomyopathy
428	ICD9	unspecified, Heart failure
I70	ICD10	Atherosclerosis
I71	ICD10	Aortic aneurysm and dissection
I73.1	ICD10	Thromboangiitis obliterans [Buerger's disease]
I73.8	ICD10	Other specified peripheral vascular diseases
I73.9	ICD10	Peripheral vascular disease, unspecified
I77.1	ICD10	Stricture of artery
I79.0	ICD10	Aneurysm of aorta in diseases classified elsewhere
I79.1	ICD10	Aortitis in diseases classified elsewhere
I79.8	ICD10	Other disorders of arteries, arterioles, and capillaries in diseases classified elsewhere
K55.1	ICD10	Chronic vascular disorders of intestine
K55.8	ICD10	Other vascular disorders of intestine
K55.9	ICD10	Vascular disorder of intestine, unspecified
Z95.8	ICD10	Presence of other cardiac and vascular implants and grafts
Z95.9	ICD10	Presence of cardiac and vascular implant and graft, unspecified
093.0	ICD9	Aneurysm of aorta, specified as syphilitic
437.3	ICD9	Cerebral aneurysm, non-ruptured
440	ICD9	Atherosclerosis
441	ICD9	Aortic aneurysm and dissection
443.1	ICD9	Thromboangiitis obliterans [Buerger's disease]
443.2	ICD9	Other arterial dissection
443.8	ICD9	Other specified peripheral vascular diseases
443.9	ICD9	Peripheral vascular disease, unspecified
447.1	ICD9	Stricture of artery
557.1	ICD9	Chronic vascular insufficiency of intestine
557.9	ICD9	Unspecified vascular insufficiency of intestine
V43.4*	ICD9	Blood vessels replaced by other means

CODE	TYPE	DESCRIPTION
G45	ICD10	Transient cerebral ischemic attacks and related syndromes
G46	ICD10	Vascular syndromes of brain in cerebrovascular diseases
H34.0	ICD10	Transient retinal artery occlusion
H34.1	ICD10	Central retinal artery occlusion
H34.2	ICD10	Other retinal artery occlusions
I60	ICD10	Non-traumatic subarachnoid hemorrhage
I61	ICD10	Non-traumatic intracerebral hemorrhage
I62	ICD10	Other and unspecified non-traumatic intracranial hemorrhage
I63	ICD10	Cerebral infarction
I64	ICD10	Stroke, not specified as hemorrhage or infarction
I65	ICD10	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	ICD10	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	ICD10	Other cerebrovascular diseases
I68	ICD10	Cerebrovascular disorders in diseases classified elsewhere
362.34	ICD9	Transient retinal arterial occlusion
430	ICD9	Subarachnoid hemorrhage
431	ICD9	Intracerebral hemorrhage
432	ICD9	Other and unspecified intracranial hemorrhage
433	ICD9	Occlusion and stenosis of precerebral arteries
434	ICD9	Occlusion of cerebral arteries
435	ICD9	Transient cerebral ischemia
436	ICD9	Acute, but ill-defined, cerebrovascular disease
437	ICD9	Other and ill-defined cerebrovascular disease
438	ICD9	Late effects of cerebrovascular disease
F01	ICD10	Vascular dementia
F02	ICD10	Dementia in other diseases classified elsewhere
F03	ICD10	Unspecified dementia
F04	ICD10	Amnestic disorder due to known physiological condition
F05	ICD10	Delirium due to known physiological condition
F06.1	ICD10	Catatonic disorder due to known physiological condition
F06.8	ICD10	Other specified mental disorders due to known physiological condition
G13.2	ICD10	Systemic atrophy primarily affecting the central nervous system in myxedema
G13.8	ICD10	Systemic atrophy primarily affecting central nervous system in other diseases classified elsewhere
G30	ICD10	Alzheimer's disease
G31.0	ICD10	Frontotemporal dementia
G31.1	ICD10	Senile degeneration of brain, not elsewhere classified
G31.2	ICD10	Degeneration of nervous system due to alcohol
G91.4	ICD10	Hydrocephalus in diseases classified elsewhere
G94	ICD10	Other disorders of brain in diseases classified elsewhere
R41.81	ICD10	Age-related cognitive decline
R54	ICD10	Age-related physical debility

CODE	TYPE	DESCRIPTION
290.0	ICD9	Senile dementia, uncomplicated
290.1	ICD9	Presenile dementia
290.2	ICD9	Senile dementia with delusional or depressive features
290.3	ICD9	Senile dementia with delirium
290.4	ICD9	Vascular dementia
294.0	ICD9	Amnestic disorder in conditions classified elsewhere
294.1	ICD9	Dementia in conditions classified elsewhere
294.2	ICD9	Dementia, unspecified
294.8	ICD9	Other persistent mental disorders due to conditions classified elsewhere
331.0	ICD9	Alzheimer's disease
331.1	ICD9	Frontotemporal dementia
331.2	ICD9	Senile degeneration of brain
331.7	ICD9	Cerebral degeneration in diseases classified elsewhere
797	ICD9	Senility without mention of psychosis
J40	ICD10	Bronchitis, not specified as acute or chronic
J41	ICD10	Simple and mucopurulent chronic bronchitis
J42	ICD10	Unspecified chronic bronchitis
J43	ICD10	Emphysema
J44	ICD10	Other chronic obstructive pulmonary disease
J45	ICD10	Asthma
J46	ICD10	Status asthmaticus
J47	ICD10	Bronchiectasis
J60	ICD10	Coal worker's pneumoconiosis
J61	ICD10	Pneumoconiosis due to asbestos and other mineral fibers
J62	ICD10	Pneumoconiosis due to dust containing silica
J63	ICD10	Pneumoconiosis due to other inorganic dusts
J64	ICD10	Unspecified pneumoconiosis
J65	ICD10	Pneumoconiosis associated with tuberculosis
J66	ICD10	Airway disease due to specific organic dust
J67	ICD10	Hypersensitivity pneumonitis due to organic dust
J68.4	ICD10	Chronic respiratory conditions due to chemicals, gases, fumes and vapors
J70.1	ICD10	Chronic and other pulmonary manifestations due to radiation
J70.3	ICD10	Chronic drug-induced interstitial lung disorders
490	ICD9	Bronchitis, not specified as acute or chronic
491	ICD9	Chronic bronchitis
492	ICD9	Emphysema
493	ICD9	Asthma
494	ICD9	Bronchiectasis
495	ICD9	Extrinsic allergic alveolitis
496	ICD9	Chronic airway obstruction, not elsewhere classified
500	ICD9	Coal workers' pneumoconiosis

CODE	TYPE	DESCRIPTION
501	ICD9	Asbestosis
502	ICD9	Pneumoconiosis due to other silica or silicates
503	ICD9	Pneumoconiosis due to other inorganic dust
504	ICD9	Pneumonopathy due to inhalation of other dust
505	ICD9	Pneumoconiosis, unspecified
506.4	ICD9	Chronic respiratory conditions due to fumes and vapors
508.1	ICD9	Chronic and other pulmonary manifestations due to radiation
508.8	ICD9	Respiratory conditions due to other specified external agents
M05	ICD10	Rheumatoid arthritis with rheumatoid factor
M06	ICD10	Other rheumatoid arthritis
M31.5	ICD10	Giant cell arteritis with polymyalgia rheumatica
M32	ICD10	Systemic lupus erythematosus (SLE)
M33	ICD10	Dermatopolymyositis
M34	ICD10	Systemic sclerosis [scleroderma]
M35.1	ICD10	Other overlap syndromes
M35.3	ICD10	Polymyalgia rheumatica
M36.0	ICD10	Dermato(poly)myositis in neoplastic disease
446.5	ICD9	Polyarteritis nodosa and allied conditions
710.0	ICD9	Systemic lupus erythematosus
710.1	ICD9	Systemic sclerosis
710.2	ICD9	Sicca syndrome
710.3	ICD9	Dermatomyositis
710.4	ICD9	Polymyositis
714.0	ICD9	Rheumatoid arthritis
714.1	ICD9	Felty's syndrome
714.2	ICD9	Other rheumatoid arthritis with visceral or systemic involvement
714.8	ICD9	Other specified inflammatory polyarthropathies
725	ICD9	Polymyalgia rheumatica
K25	ICD10	Gastric ulcer
K26	ICD10	Duodenal ulcer
K27	ICD10	Peptic ulcer, site unspecified
K28.	ICD10	Gastrojejunal ulcer
531	ICD9	Gastric ulcer
532	ICD9	Duodenal ulcer
533	ICD9	Peptic ulcer, site unspecified
534	ICD9	Gastrojejunal ulcer
B18	ICD10	Chronic viral hepatitis
K70.0	ICD10	Alcoholic fatty liver
K70.1	ICD10	Alcoholic hepatitis
K70.2	ICD10	Alcoholic fibrosis and sclerosis of liver
K70.3	ICD10	Alcoholic cirrhosis of liver

CODE	TYPE	DESCRIPTION
K70.9	ICD10	Alcoholic liver disease, unspecified
K71.3	ICD10	Toxic liver disease with chronic persistent hepatitis
K71.4	ICD10	Toxic liver disease with chronic lobular hepatitis
K71.5	ICD10	Toxic liver disease with chronic active hepatitis
K71.7	ICD10	Toxic liver disease with fibrosis and cirrhosis of liver
K73	ICD10	Chronic hepatitis, not elsewhere classified
K74	ICD10	Fibrosis and cirrhosis of liver
K76.0	ICD10	Fatty (change of) liver, not elsewhere classified
K76.2	ICD10	Central hemorrhagic necrosis of liver
K76.3	ICD10	Infarction of liver
K76.4	ICD10	Peliosis hepatis
K76.8	ICD10	Other specified diseases of liver
K76.9	ICD10	Liver disease, unspecified
Z94.4	ICD10	Liver transplant status
070.22	ICD9	Chronic viral hepatitis B with hepatic coma without hepatitis delta
070.23	ICD9	Chronic viral hepatitis B with hepatic coma with hepatitis delta
070.32	ICD9	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
070.33	ICD9	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
070.44	ICD9	Chronic hepatitis C with hepatic coma
070.54	ICD9	Chronic hepatitis C without mention of hepatic coma
070.6	ICD9	Unspecified viral hepatitis with hepatic coma
070.9	ICD9	Unspecified viral hepatitis without mention of hepatic coma
570	ICD9	Acute and subacute necrosis of liver
571	ICD9	Chronic liver disease and cirrhosis
573.3	ICD9	Hepatitis, unspecified
573.4	ICD9	Hepatic infarction
573.8	ICD9	Other specified disorders of liver
573.9	ICD9	Unspecified disorder of liver
V42.7*	ICD9	Liver replaced by transplant
E08	ICD10	Diabetes mellitus due to underlying condition
E09	ICD10	Drug or chemical induced diabetes mellitus
E10	ICD10	Type 1 diabetes mellitus
E11	ICD10	Type 2 diabetes mellitus
E13	ICD10	Other specified diabetes mellitus
250.8	ICD9	Diabetes with other specified manifestations
250.9	ICD9	Diabetes with unspecified complication
249.0	ICD9	Secondary diabetes mellitus without mention of complication
249.1	ICD9	Secondary diabetes mellitus with ketoacidosis
249.2	ICD9	Secondary diabetes mellitus with hyperosmolarity
249.3	ICD9	Secondary diabetes mellitus with other coma
249.9	ICD9	Secondary diabetes mellitus with unspecified complication, no stated an uncontrolled,

CODE	TYPE	DESCRIPTION
		or unspecified
I12.9	ICD10	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.0	ICD10	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.10	ICD10	Hypertensive heart and CKD without heart failure with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
N03	ICD10	Chronic nephritic syndrome
N05	ICD10	Unspecified nephritic syndrome
N18.1	ICD10	Chronic kidney disease, Stage 1
N18.2	ICD10	Chronic kidney disease, Stage 2 (mild)
N18.3	ICD10	Chronic kidney disease, Stage 3 (moderate)
N18.4	ICD10	Chronic kidney disease, Stage 4 (severe)
N18.9	ICD10	Chronic kidney disease, unspecified
Z94.0	ICD10	Kidney transplant status
403.00	ICD9	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified
403.10	ICD9	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified
403.90	ICD9	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified
404.00	ICD9	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.01	ICD9	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.10	ICD9	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.11	ICD9	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.90	ICD9	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.91	ICD9	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
582	ICD9	Chronic glomerulonephritis
583	ICD9	Nephritis/nephropathy
585.1	ICD9	Chronic kidney disease, Stage I
585.2	ICD9	Chronic kidney disease, Stage II (mild)
585.3	ICD9	Chronic kidney disease, Stage III (moderate)
585.4	ICD9	Chronic kidney disease, Stage IV (severe)
585.9	ICD9	Chronic kidney disease, unspecified

CODE	TYPE	DESCRIPTION
V42.0	ICD9	Kidney replaced by transplant
E08	ICD10	Diabetes mellitus due to underlying condition
E09	ICD10	Drug or chemical induced diabetes mellitus
E10	ICD10	Type 1 diabetes mellitus
E11	ICD10	Type 2 diabetes mellitus
E13	ICD10	Other specified diabetes mellitus
250.4	ICD9	Diabetes with renal manifestations
250.5	ICD9	Diabetes with ophthalmic complications
250.6	ICD9	Diabetes with neurological manifestations
250.7	ICD9	Diabetes with peripheral circulatory disorders
G04.1	ICD10	Tropical spastic paraplegia
G11.4	ICD10	Hereditary spastic paraplegia
G80.0	ICD10	Spastic quadriplegic cerebral palsy
G80.1	ICD10	Spastic diplegia cerebral palsy
G80.2	ICD10	Spastic hemiplegic cerebral palsy
G81	ICD10	Hemiplegia and hemiparesis
G82	ICD10	Paraplegia (paraparesis s) and quadriplegia
G83	ICD10	Other paralytic syndromes
334.1	ICD9	Hereditary spastic paraplegia
342	ICD9	Hemiplegia and hemiparesis
343	ICD9	Infantile cerebral palsy
344	ICD9	Other paralytic syndromes
I85.0	ICD10	Esophageal varices
I86.4	ICD10	Gastric varices
K70.4	ICD10	Alcoholic hepatic failure
K71.1	ICD10	Toxic liver disease with hepatic necrosis
K72.1	ICD10	Chronic hepatic failure
K72.9	ICD10	Hepatic failure, unspecified
K76.5	ICD10	Hepatic veno-occlusive disease
K76.6	ICD10	Portal hypertension
K76.7	ICD10	Hepatorenal syndrome
456.0	ICD9	Esophageal varices with bleeding
456.1	ICD9	Esophageal varices without mention of bleeding
456.2	ICD9	Esophageal varices in diseases classified elsewhere
572.2	ICD9	Hepatic encephalopathy
572.3	ICD9	Portal hypertension
572.4	ICD9	Hepatorenal syndrome
572.8	ICD9	Other sequelae of chronic liver disease
I12.0	ICD10	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease

CODE	TYPE	DESCRIPTION
I13.11	ICD10	Hypertensive heart and CKD without heart failure with stage 5 chronic kidney disease, or end stage renal disease
I13.2	ICD10	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
N18.5	ICD10	Chronic kidney disease, Stage 5
N18.6	ICD10	End stage renal disease
N19	ICD10	Unspecified kidney failure
N25.0	ICD10	Renal osteodystrophy
Z49	ICD10	Encounter for care involving renal dialysis
Z99.2	ICD10	Dependence on renal dialysis
403.01	ICD9	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease
403.11	ICD9	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease
403.91	ICD9	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
404.02	ICD9	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.03	ICD9	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.12	ICD9	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.13	ICD9	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.92	ICD9	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.93	ICD9	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
585.5	ICD9	Chronic kidney disease, Stage V
585.6	ICD9	End stage renal disease
586	ICD9	Renal failure NOS
588.0	ICD9	Renal osteodystrophy
V45.11	ICD9	Renal dialysis status
V45.12	ICD9	Noncompliance with renal dialysis
V56.0	ICD9	Encounter for extracorporeal dialysis
V56.1	ICD9	Fitting and adjustment of extracorporeal dialysis catheter
V56.2	ICD9	Fitting and adjustment of peritoneal dialysis catheter
V56.31	ICD9	Encounter for adequacy testing for hemodialysis
V56.32	ICD9	Encounter for adequacy testing for peritoneal dialysis
V56.8	ICD9	Encounter for other dialysis

BIOPSY AND IMAGING PROCEDURE CODES FOR CIRRHOSIS

CODE	TYPE	DESCRIPTION
47000	HCPCS/CPT-4	Biopsy of liver, needle
47001	HCPCS/CPT-4	Biopsy of liver, needle
47100	HCPCS/CPT-4	Excision procedures on the liver
0FB00ZX	ICD10 pcs	Excision of Liver, Open Approach, Diagnostic
0FB03ZX	ICD10 pcs	Excision of Liver, Percutaneous Approach, Diagnostic
0FB04ZX	ICD10 pcs	Excision of Liver, Percutaneous Endoscopic Approach, Diagnostic
0FB10ZX	ICD10 pcs	Excision of Right Lobe Liver, Open Approach, Diagnostic
0FB13ZX	ICD10 pcs	Excision of Right Lobe Liver, Percutaneous Approach, Diagnostic
0FB14ZX	ICD10 pcs	Excision of Right Lobe Liver, Percutaneous Endoscopic Approach, Diagnostic
0FB20ZX	ICD10 pcs	Excision of Left Lobe Liver, Open Approach, Diagnostic
0FB23ZX	ICD10 pcs	Excision of Left Lobe Liver, Percutaneous Approach, Diagnostic
0FB24ZX	ICD10 pcs	Excision of Left Lobe Liver, Percutaneous Endoscopic Approach, Diagnostic
5012	ICD9 pcs	Open liver biopsy
5011	ICD9 pcs	Closed liver biopsy (Closed (percutaneous) [needle] biopsy of liver)
5014	ICD9 pcs	Laparoscopic liver bx (Laparoscopic liver biopsy)
91200	HCPCS/CPT-4	Nonimaging liver elastography
76700	HCPCS/CPT-4	Complete ultrasound examination of the abdomen
76705	HCPCS/CPT-4	Ultrasound, abdominal, real time with image documentation
BF45ZZZ	ICD10 pcs	Ultrasonography of Liver
BF46ZZZ	ICD10 pcs	Ultrasonography of Liver and Spleen
8874	ICD9 pcs	Dx ultrasound-digestive (Diagnostic ultrasound of digestive system)
74181	HCPCS/CPT-4	MRI scan of abdomen
74182	HCPCS/CPT-4	MRI scan of abdomen with contrast
74183	HCPCS/CPT-4	MRI scan of abdomen before and after contrast
74185	HCPCS/CPT-4	MRI scan of blood vessels of abdomen
BF35Y0Z	ICD10 pcs	Magnetic Resonance Imaging (MRI) of Liver using Other Contrast, Unenhanced and Enhanced
BF35YZZ	ICD10 pcs	Magnetic Resonance Imaging (MRI) of Liver using Other Contrast
BF35ZZZ	ICD10 pcs	Magnetic Resonance Imaging (MRI) of Liver
74150	HCPCS/CPT-4	CT imaging of the abdomen and pelvis
74160	HCPCS/CPT-4	CT imaging of the abdomen
74170	HCPCS/CPT-4	CT imaging of the abdomen with and without IV contrast
BF2500Z	ICD10 pcs	Computerized Tomography of Liver using High Osmolar Contrast, Unenhanced and Enhanced
BF250ZZ	ICD10 pcs	Computerized Tomography of Liver using High Osmolar Contrast
BF2510Z	ICD10 pcs	Computerized Tomography of Liver using Low Osmolar Contrast, Unenhanced and Enhanced
BF251ZZ	ICD10 pcs	Computerized Tomography of Liver using Low Osmolar Contrast
BF25Y0Z	ICD10 pcs	Computerized Tomography of Liver using Other Contrast, Unenhanced and Enhanced

CODE	TYPE	DESCRIPTION
BF25YZZ	ICD10 pcs	Computerized Tomography of Liver using Other Contrast
BF25ZZZ	ICD10 pcs	Computerized Tomography of Liver
BF2600Z	ICD10 pcs	Computerized Tomography of Liver and Spleen using High Osmolar Contrast, Unenhanced and Enhanced
BF260ZZ	ICD10 pcs	Computerized Tomography of Liver and Spleen using High Osmolar Contrast
BF2610Z	ICD10 pcs	Computerized Tomography of Liver and Spleen using Low Osmolar Contrast, Unenhanced and Enhanced
BF261ZZ	ICD10 pcs	Computerized Tomography of Liver and Spleen using Low Osmolar Contrast
BF26Y0Z	ICD10 pcs	Computerized Tomography of Liver and Spleen using Other Contrast, Unenhanced and Enhanced
BF26YZZ	ICD10 pcs	Computerized Tomography of Liver and Spleen using Other Contrast
BF26ZZZ	ICD10 pcs	Computerized Tomography of Liver and Spleen
BF2C00Z	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using High Osmolar Contrast, Unenhanced and Enhanced
BF2C0ZZ	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using High Osmolar Contrast
BF2C10Z	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using Low Osmolar Contrast, Unenhanced and Enhanced
BF2C1ZZ	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using Low Osmolar Contrast
BF2CY0Z	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using Other Contrast, Unenhanced and Enhanced
BF2CYZZ	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All using Other Contrast
BF2CZZZ	ICD10 pcs	Computerized Tomography of Hepatobiliary System, All
BW2000Z	ICD10 pcs	Computerized Tomography of Abdomen using High Osmolar Contrast, Unenhanced and Enhanced
BW200ZZ	ICD10 pcs	Computerized Tomography of Abdomen using High Osmolar Contrast
BW2010Z	ICD10 pcs	Computerized Tomography of Abdomen using Low Osmolar Contrast, Unenhanced and Enhanced
BW201ZZ	ICD10 pcs	Computerized Tomography of Abdomen using Low Osmolar Contrast
BW20Y0Z	ICD10 pcs	Computerized Tomography of Abdomen using Other Contrast, Unenhanced and Enhanced
BW20YZZ	ICD10 pcs	Computerized Tomography of Abdomen using Other Contrast
BW20ZZZ	ICD10 pcs	Computerized Tomography of Abdomen

APPENDIX B. TABLE SHELLS

Table 1A: Eligibility Criteria June 2015 to December 2021 (Komodo Health Only)

Eligibility Criteria	All Patients N = XX n (%)
All patients with PBC code	
PBC diagnosis	
1 inpatient claim	
2 outpatient claims	
1 inpatient and/or 2 outpatient claims	
PBC Dx + Laboratory data	
ALP	
Bilirubin	
AST	
ALT	
ALP and Bilirubin and AST and ALT	
PBC Dx + Labs + Prescription record for UDCA	
PBC Dx + Labs + UDCA failure	
UDCA intolerant	
Inadequate UDCA response	
PBC Dx + Labs + UDCA failure + 12 months data before UDCA failure	
PBC Dx + Labs + UDCA failure + 12 months pre-index data + 12 months closed claims	
PBC Dx + Labs + UDCA failure + 12 months pre-index data + 12 months closed claims + OCA	

Table 1B: Eligibility Criteria June 2015 to December 2021 (Global PBC Registry Only)

Eligibility Criteria	All Patients N = XX n (%)
All patients with PBC diagnosis	
PBC Dx + Laboratory data	
ALP	
Bilirubin	
AST	
ALT	
ALP and Bilirubin and AST and ALT	
PBC Dx + Labs + Prescription record for UDCA	
PBC Dx + Labs + UDCA failure	
UDCA intolerant	
Inadequate UDCA response	
PBC Dx + Labs + UDCA failure + 12 months data before UDCA failure	
PBC Dx + Labs + UDCA failure + 12 months pre-index data + OCA	

Table 2: Sex of All Eligible Patients by Year

	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Sex	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Female							
Male							
Missing							

Table 3: Age of All Eligible Patients by Year

	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Age							
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 4: Race of All Eligible Patients by Year*

	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
White							
Black or African American							
Asian, Native Hawaiian or other Pacific Islander							
American Indian or Alaskan Native							
Other							
Missing							

* Note that race is not systematically reported in either database, and thus is only available on a subset of patients.

Table 5A: Region by Year (Komodo Health Only)

	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Region	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Northeast							
Midwest							
West							
South							
Missing, n (%)							

Table 5B: Patients by Country and by Year (Global PBC Registry Only)

	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Country	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
The Netherlands							
UK							
Belgium							
Germany							
France							
Italy							
Spain							
Greece							
Canada							
USA							
Argentina							
Israel							
Japan							
China							

Table 6: Index Hepatic Laboratory Values by Year (TB, ALP, ALT, AST)

Laboratory Value Statistic	All Eligible Patients						
	2016 N pts=X N index =X	2017 N pts=X N index =X	2018 N pts=X N index =X	2019 N pts=X N index =X	2020 N pts=X N index =X	2021 N pts=X N index =X	Overall N pts=X N index =X
TB							
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							
ALP							
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							
ALT							
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							
AST							
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 7: Index Platelet Counts by Year

Platelet counts	All Eligible Patients						
	2016 N pts=X N index =X	2017 N pts=X N index =X	2018 N pts=X N index =X	2019 N pts=X N index =X	2020 N pts=X N index =X	2021 N pts=X N index =X	Overall N pts=X N index =X
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 8: On UDCA Treatment by Year

On UDCA treatment	All Eligible Patients N=X
	n (%)
2016	
2017	
2019	
2020	
2021	

Table 9: UDCA Failure by Year

UDCA failure	All Eligible Patients N=X
	n (%)
2016	
2017	
2019	
2020	
2021	

Table 10: Time (Months) Since First UDCA Failure Until the Index Date (inclusive) by Year

Months since UDCA failure until index date	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 11: Clinical Evidence of Portal Hypertension (Platelets <150k; Non-Bleeding Varices; Platelets and/or Non-Bleeding Varices) by Year

Clinical evidence of portal hypertension by year	All Eligible Patients N=X
	n (%)
2016	
2017	
2019	
2020	
2021	

Table 12: Cirrhosis by Year

Cirrhosis by year	All Eligible Patients N=X
	n (%)
2016	
2017	
2019	
2020	
2021	

Table 13: Charlson Comorbidity Index Score by Year

Charlson Comorbidity Index Score by year	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
Valid, n (%)							
Missing, n (%)							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 14: Insurance Type at Index Date by Year (Komodo Health Only)

Health Insurance Type on the index date	All Eligible Patients						
	2016 N=X	2017 N=X	2018 N=X	2019 N=X	2020 N=X	2021 N=X	Overall N=X
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Commercial							
Self-insured/Exchanges							
Medicare							
Medicaid							
Dual eligible							
Other							
Missing							

Table 15: Number of Index Dates by Year

	Year						
Patients Statistic	**2016** **N=X**	**2017** **N=X**	**2018** **N=X**	**2019** **N=X**	**2020** **N=X**	**2021** **N=X**	**Overall** **N=X**
All Eligible Patients							
Patients with index date							
# index dates/patient with index date							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							
Non-OCA							
Patients with index date							
# index dates/patient with index date							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							
OCA							
Patients with index date							
# index dates/patient with index date							
Mean (SD)							
Skewness							
Median							
(Q1, Q3)							
Range							

Table 16: Sex of Patients by Group before and After Weighting

	Before Weighting		**After Weighting**	
	Non-OCA-treated	**OCA-treated**	**Non-OCA-treated**	**OCA-treated**
	N patients =	**N patients =**	**N patients =**	**N patients =**
	N index dates =	**N index dates =**	**N index dates =**	**N index dates =**
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Female				
Male				

Table 17: Age of Patients by Group Before and After Weighting

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
Age	N index dates =	N index dates =	N index dates =	N index dates =
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				

Table 18A: Region by Group Before and After Weighting (Komodo Health Only)

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
Region	n (%)	n (%)	n (%)	n (%)
Northeast				
Midwest				
West				
South				
Missing				

Table 18B: Country by Group Before and After Weighting (Global PBC Registry Only)

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
Countries in Global PBC	n (%)	n (%)	n (%)	n (%)

Table 19: Hepatic Laboratory Values by Group (TB, ALP, ALT, AST) Before and After Weighting

Hepatic Laboratory Value Statistic	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
TB				
n (%)				
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				
ALP				
n (%)				
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				
ALT				
n (%)				
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				
AST				
n (%)				
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				

Table 20: Platelet Counts by Group Before and After Weighting

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
Platelet counts	N index dates =	N index dates =	N index dates =	N index dates =
n (%)				
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				

Table 21: Patients on UDCA Treatment by Group Before and After Weighting

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
UDCA Treatment	n (%)	n (%)	n (%)	n (%)
Yes				
No				

Table 22: Duration (Months) of Receiving UDCA by Group Before and After Weighting

	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
Duration (in months) of UDCA treatment	N index dates =	N index dates =	N index dates =	N index dates =
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				

Table 23: Time (Months) from UDCA Failure Until the Index Date by Group Before and After Weighting

Time (in months) from UDCA failure until the index date	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
Mean (SD)				
Skewness				
Median				
(Q1, Q3)				
Range				

Table 24: Clinical Evidence of Portal Hypertension (Platelets <150k; Non-Bleeding Varices; Platelets and/or Non-Bleeding Varices) by Group Before and After Weighting

Clinical evidence of portal hypertension	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
	n (%)	n (%)	n (%)	n (%)
Yes				
No				

Table 25: Cirrhosis by Group Before and After Weighting

Cirrhosis	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
	n (%)	n (%)	n (%)	n (%)
Yes				
No				

Table 26: Charlson Comorbidity Index Score by Group Before and After Weighting

Charlson Comorbidity Index Score	Before Weighting				After Weighting			
	Non-OCA-treated		OCA-treated		Non-OCA-treated		OCA-treated	
	N patients =		N patients =		N patients =		N patients =	
	N index dates =		N index dates =		N index dates =		N index dates =	
Mean (SD)								
Skewness								
Median								
(Q1, Q3)								
Range								

Table 27: Insurance Type at Index Date by Group Before and After Weighting (Komodo Health Only)

Insurance type at index date	Before Weighting		After Weighting	
	Non-OCA-treated	OCA-treated	Non-OCA-treated	OCA-treated
	N patients =	N patients =	N patients =	N patients =
	N index dates =	N index dates =	N index dates =	N index dates =
	n (%)	n (%)	n (%)	n (%)
Commercial				
Medicare				
Medicaid				
Dual eligible				
Other				
Missing				

Table 28: Logistic regression for Non-OCA vs OCA-treated

Parameter	N	Estimate	SE
Non-OCA			
OCA			
Gender			
Age			
Region/Country			
Time (in months) since PBC diagnosis			
Calendar year of PBC diagnosis			
Labs			
ALP			
Total bilirubin			
ALT			
AST			
UDCA duration			
Clinical evidence of portal HTN			
Cirrhosis			
Charlson Comorbidity Index Score			
Insurance type			

Table 29: Distribution of Propensity Weights

	Non-OCA-treated	OCA-treated
	N patients =	N patients =
Propensity weights	N index dates =	N index dates =
Mean (SD)		
Skewness		
Median		
(Q1, Q3)		
Range		

Table 30: Standardized Differences of the Mean Before and After Weighting

Parameter	Standardized Mean Difference	
	Unweighted	Weighted
Gender		
Age		
Region/Country		
Time (in months) since PBC diagnosis		
Calendar year of PBC diagnosis		
ALP		
Total bilirubin		
ALT		
AST		
UDCA duration		
Clinical evidence of portal HTN		
Cirrhosis		
Charlson Comorbidity Index Score		
Insurance type		

Table 31: Results Unadjusted, Adjusted and Weighted Cox Regression on Time to Composite Event

Parameter	n	HR	95% CI	p-value
Unique cases				
Unique persons				
Cases				
Person trials				
Unadjusted				
Adjusted for baseline covariates				
Weighted				

Figure 1: Adherence to OCA Treatment over Time

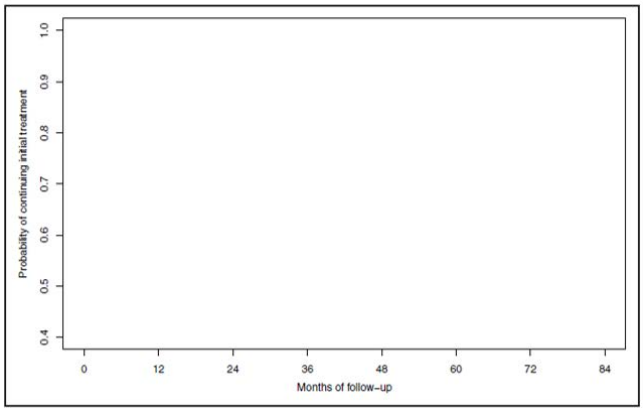

Figure 2A: Eligible Patients by Number of Trials

Figure 2B: Eligible Control Patients by Number of Trials

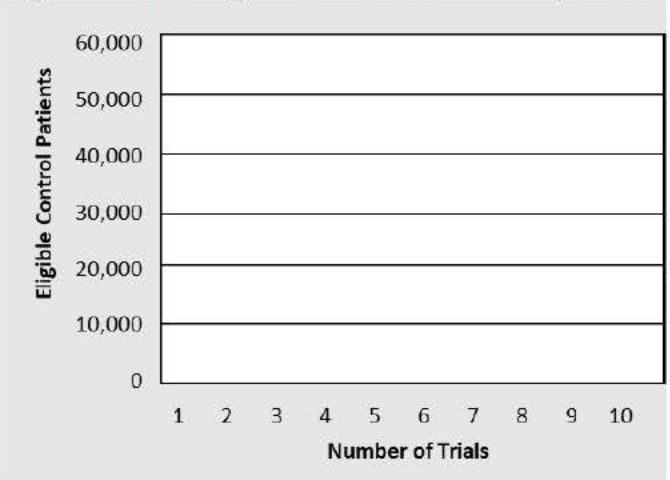

Figure 2C: Eligible OCA-treated Patients by Number of Trials

Figure 3A: Distribution of Propensity Scores: Unweighted

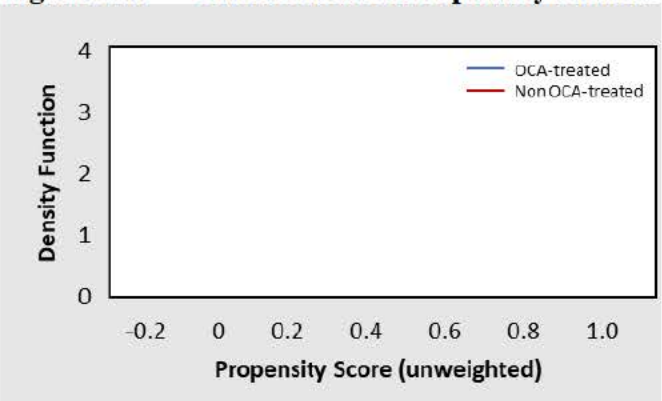

Figure 3B: Distribution of Propensity Scores: Weighted

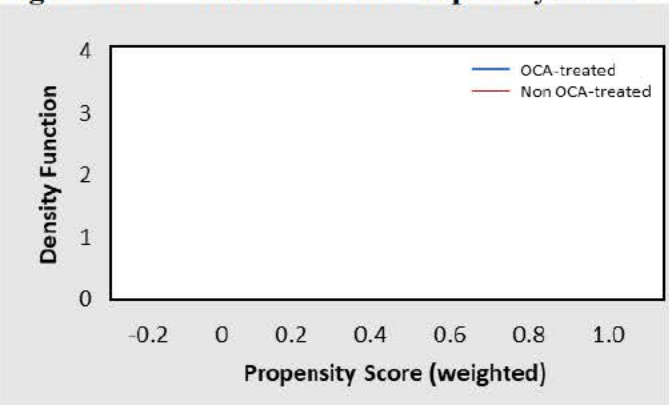

Figure 4: Kaplan-Meier Survival Curve: Composite Event-free Survival by Treatment Arm